RANDOMIZED CONTROLLED STUDY ON EFFECT OF CONCENTRATED GROWTH FACTORS ON CRESTAL BONE LEVELS AND PERI-IMPLANT BONE DENSITY IN DENTAL IMPLANTS

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CERTIFICATE

This is to certify that **Dr.V.C.KARTHIK,** Post Graduate student (2014-2017) in the Department of Prosthodontics and crown & bridge, Adhiparasakthi Dental College and Hospital, Melmaruvathur – 603319, has done this dissertation titled **"RANDOMIZED CONTROLLED STUDY ON EFFECT OF CONCENTRATED GROWTH FACTORS ON CRESTAL BONE LEVELS AND PERI-IMPLANT BONE DENSITY IN DENTAL IMPLANTS"** under our direct guidance and supervision in partial fulfilment of the regulations laid down by the Tamilnadu Dr.M.G.R Medical University, Chennai – 600032 for MDS., (Branch-I) (PROSTHODONTICS AND CROWN & BRIDGE) degree examination.

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DECLARATION

TITLE OF THE DISSERTATION	"Randomized controlled study on effect of concentrated growth factors on crestal bone levels and peri-implant bone density in dental implants"
PLACE OF THE STUDY	Adhiparasakthi Dental College and Hospital, Melmaruvathur – 603319
DURATION OF THE COURSE	3 years
NAME OF THE GUIDE	Dr.N.Venkatesan MDS.,
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I hereby declare that no part of the dissertation will be utilized for gaining financial assistance or any promotion without obtaining prior permission of the Principal, Adhiparasakthi Dental College and Hospital, Melmaruvathur – 603319. In addition, I declare that no part of this work will be published either in print or in electronic media without the guides who has been actively involved in dissertation. The author has the right to reserve for publish work solely with the permission of the Principal, Adhiparasakthi Dental College and Hospital, Melmaruvathur – 603319.

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ABSTRACT

BACKGROUND:

Modern dentistry aims to restore the comfort and health of the stomatognathic system. Dental implants have emerged as a promising option for this purpose. Concentrated growth factors (CGF) has been suggested to enhance the healing and integration of implants into bone. Growth factors are proteins which regulate the complex process of wound healing. They play an important role in cell migration, cell proliferation and angiogenesis in tissue regeneration phase. CGF was first developed by Sacco in 2006. It can be used as a barrier membrane to accelerate soft tissue healing. CGF does not require any chemical or anticoagulants so it is free from viral transmission diseases. Crestal bone levels, peri-implant bone density, bleeding, probing depth, mobility, occlusion factors, restoration adequacy, radiographic images, oral hygiene, patient health status are some of the important parameters for determining the longevity of success rates in implant dentistry. This study will assess the peri-implant bone density and crestal bone levels with and without the use of CGF.

AIM:

To evaluate the effect of concentrated growth factors on crestal bone levels and peri-implant bone density around dental implants.

MATERIALS AND METHODS:

Sampling procedure	Random selection of population (Sealed envelope method)
No.of Groups	Two Group 1- Control group Group 2- Experimental group
Sample size	20

For Group 2, implants were placed with CGF. For Group 1, implants were placed without CGF. The peri-implant bone density and bone levels were measured by Digora and signora software.

RESULTS:

Intergroup comparison (Group 1 - without CGF, Group 2 - with CGF) of mean bone level for Group 1 from mesial baseline to 1^{st} month, 3^{rd} and 6^{th} month were 0.120, 0.213 & 0.345 respectively., and Group 2 at 1^{st}, 3^{rd} and 6^{th} month were 0.074, 0.171 & 0.294 respectively (Table 3). Mean bone level for Group 1 from distal baseline to 1^{st} month, 3^{rd} and 6^{th} month were 0.133, 0.248 & 0.331 respectively and Group 2 at 1^{st} , 3^{rd} and 6^{th} month were 0.100, 0.222 & 0.320 respectively. On analyzing the results statistically, there was not significant difference between the two groups. Intragroup comparison in Group 1 and Group 2 were also not statistically significant.

Intragroup comparison of bone density values in Group 1 shows the mean difference from baseline to one month is 0.6, and after three and six months periods were 1.1 and 1.1 respectively which indicates not much significant improvement in bone density values in Group 1. In Group 2 mean difference from baseline to one month, three and six months were 2.6, 5.7 and 5.7 respectively shows significant improvement. Inter group comparison shows a significant difference between both the groups starting from as early as the 1st month.

CONCLUSION:

The results of this study indicates that CGF is significantly better in improving density of bone around the implants when comparing with non- CGF groups. Although, CGF showed improvement in bone mineralization, there is not much differences in crestal bone level changes on mesial and distal sides of the implants between two groups.

(Key words : Concentrated Growth Factor, Bone density, Crestal bone level)

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1.	ASA	-	American Society of Anesthesiologists
2.	bFGF	-	basic Fibroblast Growth Factor
3.	BMP	-	Bone Morphogenic Protein
4.	BIC	-	Bone Implant Contact
5.	CGF	-	Concentrated Growth Factor
6.	CPRP	-	concentrated Platelet Rich Plasma
7.	EGF	-	Epidermal Growth Factor
8.	FH	-	Fluoro hydroxyapatite
9.	FG	-	Fibrinogen molecules
10.	GF	-	Growth Factor
11.	HA	-	Hydroxyapatite
12.	IGF	-	Insulin like Growth Factor
13.	MCP	-	Monocyte chemotactic protein
14.	MSCs	-	Mesenchymal stem cells
15.	OPG	-	Orthopantamogram
16.	PRP	-	Platelet rich plasma
17.	PRF	-	Platelet rich fibrin
18.	PPP	-	Platelet poor plasma
19.	PDGF	-	Platelet derived growth factor
20.	PRGF	-	Platelet rich growth factor
21.	RBC	-	Red blood cells
22.	RAP	-	Regional acceleratory phenomenon
23.	RVG	-	Radiovisiography
24.	TGF	-	Transforming Growth factor
25.	WBC	-	White blood cells
26.	VEGF	-	Vascular endothelial growth factor

INTRODUCTION

Modern dentistry aims to reinstate the comfort and health of the stomatognathic system. Dental implants have emerged as a hopeful option for this purpose.[1]

Dental Implant:

A Dental implant is a prosthetic device composed of alloplastic material, placed into the oral tissues under the mucosal or/and periosteal layer, and on/or within the bone to afford retention and support for a removable or fixed dental prosthesis, a substance that is inserted into or upon the jaw bone to support a fixed or removable dental prosthesis.

A typical implant consists of a titanium screw (resembling a tooth root) with a roughened or smooth surface. Most of the dental implants are made out of commercially pure titanium available in four grades depending upon the amount of carbon and iron present. More recently grade 5 Titanium is used. Titanium 6Al-4V alloy (signifying the Titanium alloy containing 6% Aluminum and 4% Vanadium alloy) and Grade 5 Titanium are believed to provide similar osseointegration levels as commercially pure titanium. Ti -6Al-4V alloy provides better tensile strength and fracture resistance. Implant surfaces may be altered by plasma spraying, anodizing, etching or sandblasting to improve the osseointegration capacity of the implant.[2]

The origin for modern dental implant is a biologic process called osseointegration where materials, such as titanium form a close bond to bone. The implant fixture is first placed, so that it may osseointegrate, then a dental prosthesis is added. The term osseointegration has become common in implant discipline and describes both microscopic condition and clinical condition of rigid fixation.

Fibro-osseous integration – Implant Bone Interface:

The American Academy of Implant Dentistry (AAID), defined fibrous integration as “tissue-to-implant contact with healthy dense collagenous tissue between the implant and bone”. In this theory, collagen behaves similarly to Sharpey’s fibers in natural dentition. The fibers affect bone remodeling where tension is created under optimal loading conditions (Weiss). It is not accepted now as no sharpey’s fibers are present between the implant and the bone so it is difficult to transmit the loads. Therefore, bone remodeling cannot be expected to occur in fibro-osseous integration.[3]

Professor Branemark Discovery:

Professor Per-Ingvar Branemark (1952) working in the laboratory of the vital microscopy, University of Goteberg, Sweden, accidentally discovered that bone bonded well with Titanium, a phenomenon which was termed as osseointegration. In 1970s, there were no methods available to section intact bone to metal specimens. Therefore, the histological evidence of osseointegration remained indirect. Schroeder from Switzerland was the first investigator to clearly demonstrate

osseointegration by using new techniques to section bone-implant specimens. They termed this fusion as functional ankylosis.[3]

Osteointegration or osseointegration refers to a direct bone-to-metal interface without interposition of non-bone tissue. This concept was given by Branemark, as consisting of a highly differentiated tissue making "a direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant". From his initial observations on osseointegration, Per-Ingvar Branemark showed that titanium implants could become permanently incorporated within bone that is, the living bone could become so merged with the titanium oxide layer of the implant that both of them could not be divided devoid of fracture.[4]

Meffert in 1987 redefined and subdivided osseointegration as

- Adaptive osseointegration: It has an osseous tissue approximating the surface of the implant without apparent soft tissue interface at the light microscopic level.
- Biointegration: It is the direct biochemical bone surface attachment confirmed at the electron microscopic level.

Factors for Reliable Osseointegration (Albrektsson, 1983):

The factors affecting osseointegration of dental implant is critically dependent on their surface properties. Several investigations have analyzed the influence of implant surface properties for osseointegration. Topography, surface morphology, roughness, surface energy, chemical potential, strain hardening, chemical composition, the

presence of impurities, thickness of titanium oxide layer and the presence of non-metal and metal composites have a great influence on bone tissue reactions.[5]

Albrektsson insisted six factors that are particularly important for the establishment of reliable osseointegration namely implant design, implant material, status of the bone, surface conditions, surgical technique and implant loading conditions. Osseointegration can occur only if the cells adhere to the biomaterial surface. At this phase, restructuring of the cytoskeleton and information exchange between extracellular matrix and the cells at the cell-biomaterial interface occur, forming gene activation and specific tissue remodeling. Both the morphology and roughness of the biomaterial's surface have a control on cell proliferation and differentiation, extracellular matrix synthesis, local factor production and even cell morphology.[5]

Implant biocompatibility:

Metals like commercially pure titanium, tantalum and niobium are very well accepted in bone as they are covered with a very adherent, self-repairing and corrosion resistant oxide layer. Metals like cobalt-chrome-molybdenum alloys, titanium alloys and stainless steel are less well tolerated by bone. Ceramics like calcium phosphate hydroxyapatite (HA) and other types of aluminum oxides are proved to be biocompatible but due to insufficient documentation and very fewer clinical trials, they are less commonly used.[3]

Implant Design:

Threaded implants afford more functional area for stress distribution than the cylindrical implants and hence provide better primary anchorage. V-shaped threads transfer the vertical forces in an angulated path, and thus may not be as efficient in stress distribution as the square shaped threads. Longer the length, better the primary stability. Increased bone loss are associated with shorter implants (10 mm or less). Wide diameter implants exert less stress on crestal bone when compared to narrow implants. Providing micro threads at neck of the implants, helps to maintain marginal bone as these threads anchor in the bone. Whereas a smooth machined neck is allied with greater bone loss. Platform-switching concept also conserves the crestal bone and prevents bone loss. This design uses a narrow diameter abutment over a wide diameter implant. Advantages of one-piece implant over two-piece implants are elimination of Implant-abutment junction maximizes strength, eliminates micro movement and also eliminates the penetration of bacteria which might occur at the implant-abutment junction in two -piece implants.

Implant Surface:

Surface topography relates to degree of roughness of the surface and the orientation of surface irregularities. Advantages of increased surface roughness results in increased bone at surface of implant and increased biomechanical interaction of the implant with bone. Presence of smooth surfaces do not result in an acceptable bone cell adhesion and clinical failure would be prone to occur.[3]

State of the host bed:

Poor bone bed because of previous irradiation which is not an absolute contraindication for implants. However some delay is preferable before implant placement. Low height of ridge, resorption and osteoporosis are an indication for ridge augmentation with bone grafts before or during implant placement and in infection. Poor bone quality as confirmed by Branemark et al., and Misch, D1 and D2 bone densities shows good initial stability and better osseointegration while D3 and D4 exhibits poor prognosis when compared to D1 and D2.[3]

Surgical Considerations:

Surgical technique must be optimum to promote regenerative type of the bone healing rather than reparative type of the bone healing. Use of well-sharpened graded series of drills and adequate cooling is essential. Critical time/temperature relationship for bone tissue necrosis is around 47^{o} C applied for one minute. Slow drill speed (less than 2000 rotations per minute and tapping at a speed of 15 rpm with irrigation) and moderate power used at implant insertion.[3]

Loading Conditions:

Premature loading of implants will lead to anchorage of soft tissue and poor long-term function, whereas postponing the loading by means of a two stage surgery will result in bone healing and positive long term function.[3]

Use of laser and bio-active molecule on implant, systemic bone regulating hormones, modification in implant properties, local osteogenic factor and application of bone source to augment fixation were other factors which influence the osseointegration.[6]

Success criteria for Dental implants:

Success criteria of implants were proposed by Alberktsson and Misch. Crestal bone levels, peri-implant bone density, bleeding, probing depth, mobility, occlusion factors, restoration adequacy, radiographic images, oral hygiene were some of the parameters which helps in the success of implants. These criterias were widely followed at present.

Importance of Growth factors:

Growth factors are proteins which regulate the complex processes of wound healing. Growth factors play a main role on cell migration, cell proliferation and angiogenesis in tissue regeneration phase. These growth factors are mainly located in blood plasma and platelets. Platelet derived growth factor (PDGF), Transforming growth factor –β (TGF – β), Fibroblastic Growth Factor (FGF), Insulin- like growth factor I and II (IGF I & II), Bone morphogenic proteins (BMPs) were the factors mediates the healing process. Platelet concentrate such as platelet rich plasma (PRP), Platelet rich fibrin (PRF), and Concentrated growth factors (CGF) have been used to accelerate tissue healing for a long time. Among these concentrates, CGF shows better regenerative capacity than PRP and PRF.

AIM AND OBJECTIVES

The aim of this study was to assess the crestal bone levels and peri-implant bone density around dental implants with and without the application of Concentrated growth factors.

GENERAL REVIEW

Osseointegration is a direct functional and structural connection between ordered, living bone and surface of an implant carrying load. Osseointegration process observed after implant placement is compared to bone fracture healing. Direct bone healing is activated by any lesion of the preexisting bone matrix. When the matrix is exposed to extra cellular fluid, non collagenous proteins and growth factors are set to free and activate bone repair.[7]

Healing of bone with different densities:

Bone was classified by Misch as

Misch Bone Density Classification:

D1:Dense cortical bone

D2:Thick dense bone to porous cortical bone on crest & coarse trabecular bone inside.

D3:Thin porous cortical bone on the crest and fine trabecular bone inside.

D4:Fine trabecular bone pattern.

D5:Immature and non-mineralized bone.

Healing of D1 bone:

a. D1 bone is usually found in anterior mandible.

b. The cortical bone requires greater healing time compared with trabecular bone because of deprived blood circulation.

c. Healing occurs by formation of lamellar bone interface, rather than woven bone after the primary trauma. Therefore, for

complete regeneration of vital bone in this dense structure, five months healing time is required.[3]

d. However because of the load bearing capability of bone and the excellent bone implant contact, prosthetic loading of D1 bone start at very early stage.

e. Bone-implant contact (BIC) =80%.

Healing of D2 bone:

a. Usually present in anterior and posterior mandible.

b. The excellent blood supply of trabecular bone and stiff initial fixation permits adequate healing of bone within four months.

c. BIC = 70%

Healing of D3 bone:

a. Usually found in anterior maxilla

b. The time required for automatic healing is nearly 6 months. The actual implant interface develops more rapidly than D2 bone. However the extended time permits the regional acceleratory phenomenon (RAP) from implant surgery to stimulate the formation of more trabecular bone. More advanced bone mineralization in extra two months also increases its strength before loading.[3]

c. BIC =50%

Healing of D4 bone:

a. Usually found in posterior maxilla.

b. The healing and progressive bone loading sequence for D1, D2 and D3 bone requires lesser time than D4 bone which requires

more time. Time is needed not only to allow the bone to remodel at the surface but also necessary for more advanced bone mineralization and increased strength. Therefore eight months of undisturbed healing period is suggested.[3]

Fugazzotto P. A et al., demonstrated the efficacy of cylinder implant used in D4 bone. It was documented that implant success rates were much lower in D4 bone than in D1, D2 and D3.

Osseointegrated Implants - Early Tissue Response:

The various steps used in the surgical procedure cause injury and mechanical insults to both bone tissue and the mucosa. The damage to the hard and soft tissue initiates the process of wound healing which ultimately makes the implant to become “ankylotic” with the bone, i.e. osseointegrated.[3]

Lioubavina N et al., investigated the influence of initial implant stability on osseointegration between new bone generated by guided tissue regeneration and titanium dental implants and found that no osseointegration was observed between non-stabilized implants and the newly formed bone at any observation time.[3]

Tissue response to implantation:

Bone healing around implants involve a cascade of cellular and extracellular biological events take place at the bone - implant interface for healing of bone around implants until the implant surface appears finally covered with a newly formed bone. These biological

events include the activation of osteogenic processes comparable to those of the bone healing process, at least in terms of initial host response, growth and differentiation factors released by the activated blood cells at the bone-implant interface regulates this cascade of biological events. The response of the skeleton to trauma has been well studied histologically and mechanically with mounting interest in the molecular biology of this phenomenon. The host response after implantation is altered by the presence of the implant and its characteristics, the stability of the fixation and the intraoperative heating injuries which include death of osteocytes extending 100-500 µm deep into the host bone. Major stages of skeletal response to implantation related damage and histological events as related to the host response after insertion and fixation of cementless implants mechanically include formation of hematoma and mesenchymal tissue development, woven bone and lamellar bone formation through the intramembranous pathway and on the spicules of woven bone. Blood is the first biological component to come into contact with an endosseous implant. Blood cells including platelets, red cells and inflammatory cells such as polymorphonuclear granulocytes and monocytes emigrate from post-capillary venues, and migrate into the tissue surrounding the implant. The blood cells present at the implant interface are activated and release cytokines and other soluble, growth and differentiation factors. Initial interactions of blood cells with the implant influence clot formation. Platelets undergo biochemical and morphological changes as a response to the foreign surface including adhesion,

spreading, aggregation and intracellular biochemical changes such as induction of intracellular calcium increase, phosphotyrosine and hydrolysis of phospholipids. The formed fibrin matrix acts as a scaffold (osteoconduction) for the movement of osteogenic cells and eventual differentiation of these cells in the healing compartment. Osteogenic cells form osteoid tissue and new trabecular bone that finally remodels into lamellar bone in direct contact with most of the implant surface (osseointegration). Mesenchymal cells and osteoblasts seem to migrate and attach to the surface of implant from day one after implantation, depositing bone-related proteins and creating a noncollagenous matrix layer on the surface of implant that regulates binding of minerals and cell adhesion. This matrix is an early-formed calcified afibrillar layer on the implant surface, involving poorly mineralized osteoid akin to the bone cement lines and laminae limitans that forms a continuous, 0.5 mm thick layer which is rich in osteopontin, bone sialoprotein, calcium and phosphorus.[4]

Peri-implant osteogenesis:

Peri-implant osteogenesis may be in distance and in contact from the host bone. Distance osteogenesis refers to the newly formed bone trabeculae around the implant that develop from the host bone cavity towards the implant surface. But contact osteogenesis refers to the newly formed peri-implant bone that develops from the implant to the healing bone. The newly formed bone trabeculae network ensures the biological fixation of the implant and surrounds marrow bone spaces containing wide blood vessels and many mesenchymal cells. A thin

layer of calcified and osteoid tissue is deposited by osteoblasts (bone forming cells) directly on the surface of implant. Blood vessels and mesenchymal cells fill the spaces where no calcified tissue is present.[4]

Murai et al., were the first to report a 20-50 millimeter thin layer of flat osteoblast-like cells, a slight mineralized area and calcified collagen fibrils at a Titanium implant-bone interface. The newly formed bone was laid down on the reabsorbed surface of the old bone after osteoclastic activity. This stated that the implant surface is positively recognizable from the osteogenic cells as a biomimetic scaffold which may support early peri-implant osteogenesis. Cement lines of poorly mineralized osteoid separated the area where bone formation initiated and bone reabsorption was completed. A few days after implantation, even osteoblasts in direct contact with the implant surface began to deposit collagen matrix directly on the early formed lamina limitans layer or cement line on the implant surface. Osteoblasts cannot always migrate so rapidly to avoid being completely surrounded by the mineralizing front of calcifying matrix. These osteoblasts became clustered as osteocytes in bone lacunae. The early deposition of new calcified matrix on the implant surface is followed by the arrangement of the bone trabeculae and woven bone. This is appropriate for the peri-implant bone healing process as it shows a very active wide surface area, contiguous with marrow spaces rich in vascular and mesenchymal cells. Mononuclear precursors of osteoclasts are supported by the marrow tissue containing a rich vasculature supports and hence the bone trabeculae remodel faster than cortical

bone. Initially, rapid woven bone formation occurs on implants to restore continuity, though its mechanical capability is lower compared to lamellar bone based on the random orientation of its collagen fibers. Trabecular and woven bone fill the initial gap at the bone-implant interface. Being arranged in a three-dimensional regular network, it offers a high resistance to early implant loading. Its physical structural design including arches and bridges offers a biological scaffold for cell attachment and bone deposition that is biological fixation. The early peri-implant trabecular bone formation assures tissue anchorage that corresponds to biological fixation of the implant. This begins at 10 to 14 days after surgery. Biological fixation differs from primary stability that is easily obtained during the implant insertion. Biological fixation of the implant involves biophysical conditions such as primary stability that is implant mechanical fixation, biomimetic implant surface and right distance between the implant and the host bone. It is prevalently observed in rough implant surfaces.[4]

Subsequently, woven bone is progressively remodeled and substituted by lamellar bone that will reach a high degree of mineralization. At three months post-implantation, a mixed bone texture of woven and lamellar matrix can be found around various types of titanium implants. Peri-implant bone which contains regular osteons and host bone chips enveloped in mature bone. The implant surface is enclosed with flattened cellsak. The bone-implant interface shows inter-trabecular marrow spaces delimited by surface of the titanium from one side and by newly formed bone from the other one

rich in blood vessels and cells. Host bone chips between the implant and the host bone cavity presumably occur from the surgical bur preparation or implant insertion. These are enveloped in a newly formed peri-implant trabecular bone, and appear to be involved in trabecular bone formation during the first weeks, i.e., in the biological fixation of the implant, by improving and guiding peri-implant osteogenesis as osteoconductive and osteoinductive biological material.[4]

The most important factors for the failure of peri-implant osteogenesis include the reduced number and/or activity of osteogenic cells, the increased osteoclastic activity, the imbalance between catabolic and anabolic local factors acting on bone formation and remodeling, the abnormal bone cell proliferation rate and response to local and systemic stimuli and mechanical stress and the impaired vascularization of the peri-implant tissue. Vascularization is of decisive importance for the process of osseointegration. Differentiation of osteogenic cells strictly depends on vascularity of the tissues. Ossification is also closely related to the revascularization of the differentiating tissue. Since aging impairs angiogenesis, biomaterial osseointegration is reduced. In the elderly, the association of impaired angiogenesis with osteoporosis increases the risk of implant failure.

Peri-implant bone remodeling:

Bone in contact with the implant surface undergoes morphological remodeling as adaptation to stress and mechanical

loading. The presence of medullary or marrow spaces containing osteoblasts, osteoclasts, mesenchymal cells and lymphatic/blood vessels next to the implant surface confirms the turnover of peri-implant mature bone in osseointegrated implants. New osteons encircle the implant with their long axes parallel to the implant surface and perpendicular to the long axis of the implants during the remodeling of the peri-implant bone. Osteoid tissue is produced by osteoblasts suggesting that osteogenesis is happening. The remodeled bone can extend up to 1 mm from the implant surface.[4]

Success Criteria for Dental implants:

The important function of a dental implant is to act as an abutment for a prosthetic device, comparable to a natural tooth root and crown. Any success criteria, therefore, must include first and foremost support of a functional prosthesis.[8] Success criteria for endosteal implants proposed by Albrektsson et al., is widely used nowadays. In 1993, an implant quality of health scale was formed by James and further developed by Misch. On 5th October, 2007, a Pisa, Italy Consensus Conference (supported by the International Congress of Oral Implantologists) modified the James-Misch Health Scale and permitted four clinical category that contain conditions of implant success, survival and failure. The Four Main Categories identified as Parameters for success were related to the implant level, peri-implant soft-tissue level, prosthesis level, and the patient's subjective assessment. Success in implant dentistry should ideally evaluate a long-term primary outcome of an implant-prosthetic complex as a

whole.[9] Crestal bone levels, peri-implant bone density, bleeding, probing depth, mobility, occlusion factors, restoration adequacy, radiographic images, oral hygiene, patient health status are some of the important parameters for determining the longevity of success rates in implant dentistry. Periodontal indices are used often for the evaluation of dental implants. Periodontal indices do not define implant success or failure by themselves. These clinical indices must be related to other factors such as exudates or excess loading of the prosthesis.[8]

Pain:

Pain or tenderness associated with an implant body are more difficult to assess. Once the implant has achieved primary healing, the primary subjective criterion is the absence of pain under perpendicular or parallel forces. After healing, pain should not be present with the implant. If it is present, it is more often an inappropriate fitting of prosthetic component, or it may be due to the pressure on the soft tissue from the prosthesis. Percussion and forces up to 500 g may be used clinically to estimate implant pain or discomfort. Percussion is used for the impact force to the implant, not for the audible outcome linked with integration. Pain during function from an implant body is a subjective criterion that places the implant in the unsuccessful category. Sensitivity from an implant on working may place the implant in the survival criteria, and may necessitate some clinical management.[8]

Mobility:

A clinical term for implants namely rigid fixation, describes the absence of observed clinical mobility with vertical or horizontal forces under 500 g, similar to evaluating teeth. Osseointegration or osteointegration is a histologic term which is defined as the surrounding bone in direct contact with the surface of an implant at the magnification of a light microscope. Over the years, osseointegration and rigid fixation have been used interchangeably. Today, the clinical term “lack of mobility” may be used to explain implant movement, and is a clinical condition most often used to determine as to whether the implant is integrated. Lack of movement clinically does not mean the true absence of mobility. A healthy implant may possibly move less than 75 µm; yet, it appears as zero clinical mobility. Clinical lack of implant mobility does not always coincide with a direct bone-implant interface. But when observed clinically, lack of mobility usually means that atleast a portion or part of the implant is in direct contact with bone, although the percentage of bone contact cannot be specified.[8]

Radiographic Crestal Bone Loss:

The marginal bone around the crestal region of an implant is usually a noteworthy indicator of implant health. The crestal bone level may be measured from the crestal position of the implant at the initial implant surgery. The most common method to asses bone loss after healing is by radiographic evaluation. Conventional radiographs monitor the mesial or distal aspect of bone loss around the implant body. Several studies report yearly marginal bone loss after the first

year of function in the range of 0 to 0.2 mm radiographically. Clinical observations obtained by probing or measurements by radiograph of 0.1 mm for bone loss are operator sensitive and usually are not reliable. The bone loss measurement should be related to the original marginal bone level at implant insertion, rather than to a previous measurement (e.g.1 year before). Conventional periapical radiograph method is the most common method used to assess the marginal bone loss. Though this determines the mesial and distal bone loss, it is a time-tested method.[8]

Probing Depths:

Probing depths around teeth are a tremendous established means to assess the past and present health of natural teeth, but probing depths around implants may be of small diagnostic value, if it is not accompanied by signs (e.g., purulent exudates, radiographic radiolucencies, bleeding) and/or symptoms (e.g., pain, discomfort). Increasing probing depths for a long time may indicate bone loss, but not essentially indicate disease for an endosteal implant. Stable, rigid, fixated implants have been reported with pocket depths ranging from 2 to 6 mm. Lekholm et al., found that the presence of deep pockets was not accompanied by accelerated marginal bone loss. Healthy, partially edentulous implant patients consistently show signs of greater probing depths around implants than teeth. Probing pressures are subjective, as is the angulation of the probe next to an implant crown. The “correct pressure” for probing has not been defined for implants, but will be

less important than with teeth, because of absence of connective tissue attachment zone next to an implant.[8]

Peri-implant Disease:

The term peri-implantitis describes the bone loss from bacteria around an implant. Peri-implantitis is defined as an inflammatory process affecting the tissue around an implant in function that has resulted in loss of supporting bone. Bacteria, on occasion, may be the primary factor for bone loss around an implant. Anaerobic bacteria have been observed in the sulcus of implants, especially when probing depths are greater than 5 mm. Stress-induced bone loss (e.g., overloading the bone implant interface) occurs without bacteria as the primary causative agent. However, once the bone loss from bacteria or stress deepens the sulcular crevice and decreases the oxygen tension, anaerobic bacteria may become the primary promoters of the continued bone loss. In other words, the bacteria involved in peri-implantitis may be secondary to one of the prime causative factors, such as overloading the bone-implant interface. An abscess around an implant or exudate indicates exacerbation of the peri-implant disease and possible increased bone loss. An exudate persisting for more than 1 to 2 weeks usually requires surgical revision of the peri-implant area to eliminate causative elements. Reduction of bone height, after the exudate episode, makes the implant more prone to secondary occlusal trauma.[8]

BLOOD DERIVED BONE AUGMENTATION FACTORS – GROWTH FACTORS:

Evolution of growth factors:

Growth factors are biological mediators that regulate key events in repair of tissues such as chemotaxis, differentiation, proliferation and cellular synthesis. Growth factors have a direct autocrine or paracrine effect. Their action is performed through specific receptors on surfaces of cell membrane ultimately leading to target cells metabolism modifications. In 1971, Urist addressed the role of bone morphogenic proteins (BMP) in osteoinduction. In 1988, Woney et al., succeeded in cloning the genes which codes for BMP.[10] This lead to the discovery of growth factors which contribute to bone regeneration. Growth factors used in osseointegration mechanism are

a) Platelet derived growth factor (PDGF)
b) Transforming growth factor –β (TGF – β)
c) Fibroblastic Growth Factor (FGF)
d) Insulin- like growth factor I and II (IGF I & II)
e) Bone morphogenic proteins (BMPs)

Platelets and plasma concentrates contain high quantities of growth factors. Various techniques are used to obtain different ratios of platelets namely

- Platelet rich plasma (PRP)
- Platelet rich fibrin (PRF)
- Concentrated Growth Factors (CGF)

Platelet rich plasma (PRP) is the first generation platelet concentrate used to accelerate tissue healing. Platelet rich fibrin (PRF) was developed by Choukroun in 2001. Lastly Concentrated growth factor (CGF) was developed by Sacco in 2006.

Platelet derived growth factor (PDGF):

It is a main healing hormone. In bone culture, PDGF stimulates mitogenic and chemotactic activities as well as protein synthesis. It is secreted by different cell types like, platelets, osteoblasts and activated macrophages. Several in vitro and in vivo studies suggest that PDGF and IGF –1 are synergistic and more efficient when mixed together in promoting cell proliferation and formation.[10] PDGF found in other cells such as macrophages, endothelial cells, monocytes and fibroblasts.[11] Dog and primitive studies, using the combination PDGF and IGF -1 showed increased bone regeneration which was translated into significant bone filling. Other studies have also shown that this combination promotes bone formation in extraction sockets surrounding implant. Finally naturally rich in PDGF, platelet rich plasma PRP has proven useful in healing of autologous bone grafts.[10]

Transforming growth factor-β (TGF-β):

It is present at the level of the bone matrix and stimulate extracellular and collagen Type 1 matrix.[12] Regeneration of bone increased by transforming growth factor-β (TGF-β) seems to dependent on the presence of the cells engaged in an osteoblastic function. TGF-β

applied at the same time an inserting a dental implant increases osseointegration.[10]

Fibroblastic Growth Factor (FGF):

FGFs are classified as acidic or basic factors. They are present in bone matrix and act as mitogenic and chemotactic factors for osteoblasts. They promote bone cell formation, as well as angiogenesis. Basic FGFs seems to be more potent and can stimulate other growth factors. Even though the number of osteoblasts is increased by fibroblastic growth factors, it decreases the quantity of matrix formed. However, bone formation is still viewed as a beneficial effect of FGF. FGFs are unique factors because of their angiogenic effect, whereby they stimulate blood vessel formation, which is essential for wound healing.[10]

Insulin-like growth factor I and II (IGF I & II):

IGF I and II are present in bone and have a parallel action but are autonomously synchronized. More abundant than IGF I, IGF II is less effective as a promoter of bone formation. IGF I is produced by osteoblasts and stimulates bone formation by differentiation, proliferation and biosynthesis.[10]

Giannobile et al., demonstrated the synergistic mitotic effects on osteoblasts of IGF I and other factors (FGF, PDGF, TGF-β). Finally when associated with other factors, IGF I and II clearly potentiate the process of bone healing.[10]

Bone morphogenic proteins (BMPs):

BMPs can be obtained from bovine bone by dissociated extraction, which is a delicate process that does not give a certified homogeneous biochemical product because of the presence of the contaminants. Moreover, the quantities obtained relative to bone mass are always low (0.1 mg BMP/g bone).[10] Using recombinant DNA can help to avoid such issues. This genetic process encodes for the desired proteins. Gene isolation is carried out by identification of the mRNA replicated during protein synthesis. Once the mRNA is isolated, it can be transcribed into DNA by reverse transcriptase enzyme. Complementary DNA is used by the cellular system for protein production.[10] Utilization of a Chinese hamster ovarian cell line can produce a purified human protein, recombinant human BMP-2 (rhBMP-2). This process allows the accurate transcription of non-contaminated protein with real properties and in unlimited supply.[10]

Structurally, BMPs are part of TGF-β family and in contrast to other growth factors, are able to induce new bone formation and the major effect is to induce differentiation of multipotent cells that produce bone and cartilage.[10] BMPs are synergistic with IGF I in the differentiation and proliferation of osteoblasts. During the past two decades, atleast 20 different BMPs have been identified, such as BMP-2, BMP-3 (osteogenine), BMP-4 and BMP-7.[10] BMPs are abundant in bone and are produced by many cell types and osteoblasts in particular. However their production rate is variable, which might partially

explain the contradictory results of bone regeneration in in vivo studies using lyophilized and dried bone allografts.[10]

It seems that bone regeneration results are better with larger quantities of BMPs. In vitro studies have shown the promotion effects of BMPs on bone regeneration. Several animal studies have confirmed the in vitro results and shown that BMPs induce more regeneration in surgical lesions than in control untreated lesions. This treatment currently has the greatest potential for bone reconstruction therapy.[10]

BMP-1	Protease, activates BMPs, non- osteoconductive
BMP-2	Osteoinductive, differentiates osteoblasts , localized in bone
BMP-3 (osteogenine)	Osteoinductive
BMP-4	Osteoinductive, action in fracture healing
BMP-5	Osteoinductive
BMP-6	Non-osteoinductive
BMP-7 (osteogenic protein-1 or OP-1)	Osteoinductive, action in alveolar bone repair and osteoblast differentiation
BMP-8 (OP-2)	Osteoinductive
BMP-8B (OP-3)	
BMP-9	Osteoinductive

Platelet rich plasma:

PRP is a prosperous source of growth factors.[13] It is an autologous source of platelet derived growth factor and transforming growth factor β.[14] Under sterile condition, 6 ml of blood was drawn intravenously from the anticubital fossa region of patient's forearm using blood collecting needle and vacutainers (each 6 ml) containing of 3.8% tri-sodium citrate (0.8 ml each). The vacutainers were thoroughly moved to and fro to make sure mixture of anti-coagulant with the drawn blood. The whole blood was then centrifuged for around ten minutes at 2,400 rpm. The supernatant formed was platelet poor plasma (PPP) and buffy coat. PPP and buffy coat [upper 1 mm red blood corpuscles (RBC)] layer was collected in a fresh vacutainer and centrifuged again at 3,600 rpm for 10 minutes. The upper half of the supernatant was removed and the lower half was mixed completely to obtain PRP. PRP activation was done with addition of 10% calcium gluconate to form PRP gel.[15] PRP enhances both hard and soft tissue healing through concentrated platelets.[16] PRP gel is formed by mixing PRP with thrombin and calcium chloride.[17] Concentrated PRP can be prepared by further centrifugation of PRP.[18] PRP modulates cell proliferation in a cell type specific manner.[19] The use of PRP in combination with autologous bone led to increased bone regeneration and bone density.[20] Further PRP in combination with mesenchymal stem cells enhance bone formation.[21]

Platelet rich fibrin:

Under aseptic conditions, 6 ml of blood was drawn intravenously from the anticubital region of patient's forearm using vacutainer needle and transferred into vacutainers without using the anticoagulant. The blood sample which was taken without anticoagulant in tubes was instantly centrifuged for ten minutes at 3,000 rpm. The absence of anticoagulant starts the activation in a few minutes of most platelets of the blood sample in contact with the walls of the test tube and the release of the coagulation cascades. Initially fibrinogen was concentrated in the high part of the tube, before the circulating thrombin transformed it into the fibrin. A fibrin clot was then obtained in the middle of the tube, between the red corpuscles at the bottom and cellular plasma at the top.[15] A PRF blood clot contains 4% RBC's, 95% platelets and 1% WBC's.[22] PRF can be used along with bone grafts which promotes bone growth and maturation.[23]

Concentrated Growth Factors:

The preparation of Concentrated growth factor is simple. Compared to Platelet rich fibrin, Concentrated growth factor is attained by single centrifugation using special centrifuge.[24] CGF has been suggested to enhance the healing of bone grafts and enhance the integration of implants into bone. It can be used as a barrier membrane to accelerate soft tissue healing. Concentrated growth factor does not require any chemical or anticoagulants so it is free from viral transmission diseases. Concentrated growth factor is 100% autologous. Unlike Platelet rich plasma, Concentrated growth factors is well known

to accelerate healing. Concentrated growth factors is also an alternative to bone substitutes in sinus augmentation. One step protocol is needed to obtain Concentrated growth factors from blood sample unlike platelet rich plasma bone formation.[24]

Surgeons use Concentrated growth factors as barrier membrane to accelerate soft tissue healing or can be mixed with bone graft to accelerate new bone formation. Whether the use of CGF to enhance Osseointegration, thus leading to better success of implants is yet to be studied.[24] Comparing platelet concentrates, Concentrated growth factors exhibits better regenerative capacity and higher versatility. It shows greater tensile strength, good amount of growth factors, higher viscosity and higher adhesive strength.[25]

REVIEW OF LITERATURE

R E Marx et al (1998)[14], found that the Platelet-rich plasma is an autologous source of platelet-derived growth factor and transforming growth factor beta that is obtained by sequestering and concentrating platelets by gradient density centrifugation. This technique produced a concentration of human platelets of 338% and identified platelet-derived growth factor and transforming growth factor beta within them. Monoclonal antibody assessment of cancellous cellular marrow grafts demonstrated cells that were capable of responding to the growth factors by bearing cell membrane receptors additional amount of growth factors obtained by adding PRP to grafts evidenced a radiographic maturation rate 1.62 to 2.16 times that of grafts without platelet- rich plasma.

P Edward Anitua MD, DDS et al (1999)[11], found that the use of platelet rich growth factor provides conditions for obtaining more rapid and effective bone regeneration. Platelet rich growth factor gel which is a coagulated mass is easy to manipulate, but it must be applied without delay to preserve growth factor activity. In addition to these growth factors, other proteins carried platelets may act with other cytokines released from other cellular sources, modulating hemostasis. These results suggest that reinforcing growth factor concentration through the application of PRGF in the wound improves soft tissue repair and bone regeneration. No negative effect has been found and

the epithelialisation has been complete and significantly better than in areas not treated with PRGF.

A.Dugrillonetal et al (2002)[18], concluded that platelets are rich in growth factors and may contribute to an accelerated tissue regeneration process. The therapeutic osteogenic effect of local platelet administration probably depends on the amount of growth factors delivered within. To improve platelet-derived factor preparations, the platelets have to be concentrated without loss of the granular growth factor load. An autologous procedure according to the Good Manufacture Practice (GMP) guidelines to prepare a high concentrate from platelet-rich plasma (cPRP) for clinical application in bone regeneration is necessary.

Michael Tischler DDS et al (2002)[16], concluded that the application of PRP offers the patient something that is safe from outside disease transmission or immunogenic reactions. PRP preparation can be easily obtained in dental office environment and can be used for various procedures being done. The growth factor enhancement is especially applicable for patients who are healing impaired such as elderly. Platelet rich plasma appears to enhance both hard tissue and soft tissue healing through concentrated platelets and growth factors such as platelet derived growth factor (PDGF) and Transforming growth factor β (TGF–β).

Kazuhiro et al (2003)[19], concluded that PRP has been thought, but not well demonstrated, to contain certain growth factors, such as PDGF and TGF-β, at high concentrations. In general, it has not been demonstrated that these growth factors in PRP are involved in accelerating regeneration of periodontal tissue damaged by periodontitis. This study for the first time shown the PRP containing these growth factors efficiently and effectively regulated the proliferation of periodontal related cells in culture.

G Weibrich et al (2004)[20], concluded that PRP seems to be able to activate the osseous regeneration processes under optimized conditions. The simulatory effect of PRP in vitro on the proliferation of osteoblasts seems to start in vivo in the second week, can be evaluated statistically significant from the third week, and still exists in the fourth week. The platelet concentration required for a positive PRP effect seems to span a small range of concentration. Advantageous biological effects seem to appear when PRP with a platelet concentration of approximately 1000000/µl is used. At lower concentration the effect is suboptimal while higher concentration might have a paradoxically inhibitory effect.

R L Eppley et al (2004)[12], found that the platelets can be sequestered and concentrated eight fold from whole blood without activating the platelets before desired. These platelets contain a host of growth factors, such as PDGF-BB, TGF-[beta] 1, VEGF and EGF, whose levels are increased when platelets are concentrated into

platelet-rich plasma gel preparations. Platelet-rich plasma, and the associated fibrin clot, can potentially aid in wound repair and help to maintain hemostasis, or can be mixed with other tissues as an adjunct to their transplantation. However growth factor concentration varied from patient to patient. Sufficient concentrates and release of these growth factors through autologous platelet gels may be capable of expediting wound healing.

Khoury et al (2006)[10], concluded that promising accelerated osseointegration results have been obtained with Platelet rich plasma at implant sites, which is regarded as a very interesting finding in maxillary areas, fracture sites type IV bone and in females with osteoporosis. Moreover soft tissue heals better with platelet rich plasma. The platelet gel is more frequently used in reconstructive and plastic facial surgery and provides greater patient comfort. It is probable that tissue engineering and genetic therapies modify implant and regenerating strategies if all ongoing studies confirm such results.

Hesham El-sharkawy et al (2007)[13], found that Growth factors were increased significantly in PRP compared to whole blood (WB) and platelet-poor plasma. Monocyte chemotactic protein-1 (MCP-1) was suppressed significantly by PRP, whereas regulated on activation, normal T-cell expressed and secreted RANTES was increased significantly in monocyte cultures. LXA (4) levels were significantly higher in PRP compared to WB. PRP stimulated monocyte chemotaxis in a dose-dependent fashion, whereas RANTES, in part, was

responsible for PRP-mediated monocyte migration. Platelet rich plasma promotes regeneration of bone presumably through the action of CGF. However it is not clear how PRP affects the inflammatory response.

Pieri F et al (2008)[21], found that autologous, allogenic and alloplastic materials for sinus augmentation have specific drawbacks, which has stimulated an ongoing search for new materials and tissue-engineering constructs. Mesenchymal stem cells (MSCs), platelet rich plasma (PRP) and Fluorohydroxyapatite (FH) scaffold (test site) or FH alone (control site) were grafted in each maxillary sinus. Distal to the osteotomy, one dental implant per sinus was placed in the grafting material through the facial sinus wall. The animals were killed 3 months after grafting, and block sections of the implant sites were harvested and prepared for histomorphometric analysis. After 12 weeks, a significant increase in bone formation occurred in the test sites compared with the control sites. In addition, Bone-implant contact (BIC) was significantly greater in the test sites compared with the control sites in the regenerated area which shows that sinus augmentation with MSCs–PRP, combined with FH may enhance bone formation and osseointegration of dental implants compared with FH alone in minipigs.

Carl E. Misch DDS, MDS et al (2008)[8], concluded that Implant success is as difficult to describe as the success criteria required for a tooth. A range from health to disease exists in both conditions. The primary criteria for assessing Implant quality, or health are pain and

mobility. The presence of either one greatly compromises the implant survival and removal usually is indicated. Routine probing depths are not suggested in the absence of other signs or symptoms and may be related to the presence of local disease or pre existing tissue thickness before the implant was inserted. Bone loss is most often evaluated with radiographs, which only monitor the mesial and distal marginal bone next to the implant. Implant failure is easier to describe than implant success or survival and may consist of a variety of factors. Any pain, vertical mobility, and uncontrolled progressive bone loss warrant implant removal.

A.F. Mavrogenis et al (2009)[4], concluded that cell types, implant and bone tissues, growth factors and cytokines are involved in a co-ordinated manner during the inflammatory, formation and remodeling phases of bone healing. This means that osseointegration should be regarded not as an exclusive reaction to a specific implant material but as the expression on the endogenous basic regenerative potential of bone. The final goal is controlled, guided, and rapid peri-implant bone healing which leads to fine and fast osseointegration for direct structural and functional connection between living bone and the surface of an implant into bone allowing early implant loading cell types, implant and bone tissues, growth factors and cytokines are involved in a co-ordinated manner during the inflammatory, formation and remodelling phases of bone healing.

Dong-seok sohn et al (2009)[24], stated that regardless of bone graft materials used, augmented maxillary sinus with variable bone grafts has been considered a prerequisite for the achievement of clinical success of implants placed into augmented maxillary sinus. However, successful new bone formation and osseointegration of implants were recently reported in the lateral approaches with performing sinus membrane elevation without bone grafts. Bone substitutes may not be prerequisites for sinus augmentation according to author's study. However similar healing period was needed for consolidation of new bone in the sinus. When applying CGF alone without bone substitutes for sinus augmentation, CGF may accelerate new bone formation in the sinus. In addition, CGF can be applied for guided bone regeneration, soft tissue healing, periodontal surgery and any other oral surgery associated with bony defects in order to reduce healing time and cost for bone materials and barrier membranes.

Dong-seok sohn et al (2009)[25], found that growth factors play a major role to repair or generate damaged tissue. Most of growth factors are in blood plasma and platelet. So platelet concentrates contains sufficient growth factors such as platelet derived growth factors (PDGF), transforming growth factor-beta (TGF-β), Insulin-like growth factor (IGF-I), epidermal growth factor(EGF), vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). PRP has widely been used in the dental field such as sinus augmentation, ridge augmentation, periodontal regeneration and soft tissue healing. However the effect of PRP is controversary. According to one systemic

review on the effect of PRP, the beneficial effects of PRP in the treatment of periodontal defects is evident but evidence for beneficial effects of PRP in sinus elevation appeared to be weak.

Carlos Nelson Elias et al (2010)[5], concluded that various processes exist to treat the surface of commercially available implants. Most of these surfaces have been analyzed by in vivo and in vitro studies, showing high clinical success rates. However, the methodologies used to prepare these surfaces are mostly empirical, requiring a great number of assays. Moreover, the tests are not standardized and this makes it difficult to compare the results. The results from in vivo and in vitro studies show that the surface characteristics of the dental implants influence cell activity. The dental implant surface treatment influences the way cells adhere to the surface, which influences differentiation, proliferation, differentiation and formation of extracellular matrix.

Dr.Manimaran et al (2010)[17], found that the properties of Platelet rich plasma are based on the activation and release of multiple growth factors upon activation. They enhance and accelerate soft tissue healing and bone regeneration. Owing to the availability of these growth factors in high concentration of platelets, use of Platelet rich plasma offers distinct advantages over other media containing natural or recombinant factors. The action of these factors are very complex because individual action on same tissues vary depending upon local

factors and interaction between one another. Most of the advantages regarding PRP are still in research.

Dr.Kiran NK et al (2011)[23], concluded that the affinity of osteoblasts to the PRF membrane appeared to be superior. PRF has many advantages over PRP. It eliminates the redundant process of adding anticoagulant as well as the need to neutralize it. The addition of bovine derived thrombin to promote conversion of fibrinogen to fibrin in PRP is also eliminated. The elimination of these steps considerably reduces biochemical handling of blood as well as risks associated with the use of bovine derived thrombin. Platelet rich fibrin has more advantages over platelet rich plasma and very favourable to the healing process due to slow polymerisation reaction.

DS Sohn et al (2011)[30], found that platelet aggregates, such as platelet-rich plasma and platelet-rich fibrin gel in CGFs, have been used to accelerate new bone formation associated with guided bone regeneration and sinus grafting for many years. Fibrin-rich gel is known to release growth factors, such as transforming growth factor 1, platelet derived growth factor, vascular endothelial growth factor and accelerates new bone formation when combined with bone grafting in the maxillary sinus. In addition, fibrin-rich blocks with CGFs as the sole material acted as an alternative to bone grafting and induced fast new bone formation in the sinus. Compared with platelet-rich plasma or platelet-rich growth factors, fibrin rich blocks with CGFs are simple to make and do not require any synthetics or biomaterials, such as

bovine thrombin. According to this study, bone graft material may not be a prerequisite for sinus augmentation. Insertion of fibrin-rich blocks with CGFs as an alternative to bone grafting and simultaneous implantation showed successful new bone formation in the sinus and can be a predictable procedure for sinus augmentation and calcium chloride, to make gel, so it is free from the risk of cross-contamination.

Dragana Gabric Panduric et al (2011)[28], concluded that Computer aided densitometric image analysis (CADIA) measurement were described and its values were in strong correlation with Computed Tomography (CT) values. Described CADIA modification is designed to monitor changes in bone density around implants and to compare it with other images. If there is a need to precisely determine a densitometric value, original stepwedge is inevitable, CADIA measurement were follow-up with Osstell device which was helpful tool for determination of primary stability. Primary implant stability is in strong correlation with implant success.

G.O. Gallucci et al (2011)[9], concluded that the four most frequently used parameters for assessing success were identified related to implant level, peri-implant soft tissue, prosthesis and patient's subjective evaluation. These parameters were the most commonly used in the dental literature that was systematically reviewed. An attempt to list these parameters in the order of importance seems difficult, because successful osseointegration as the

baseline and milestone of implant therapy cannot be directly compared with patient satisfaction, which is equally important. Another issue that needs to be addressed is a patient centered outcome and patient satisfaction with prosthesis at implant level, peri-implant soft tissue, prosthesis and patient's subjective evaluation are the four more frequently used parameters for assessing implant success.

Dr. T.V. Padmanabhan et al (2013)[7], concluded that the endosseous dental implant has become a scientifically accepted and predictable treatment for completely and partially edentulous patients. Successful osseointegration is a prerequisite for functional dental implants. The osseointegration is a complex process that can be influenced by many factors relating to the surface topography, biocompatibility and loading conditions all play an important role in osseointegration. Titanium and its alloys are the materials of choice clinically, because of their excellent biocompatibility and superior mechanical properties. The combined effect of surface energy, surface roughness, and topography on implant determines its ultimate ability to integrate into the surrounding tissue. Surface modification technologies involve preparation with either an additive coating or subtractive method. Cell migration, adhesion and proliferation on implant surfaces are important prerequisites to initiate the process of tissue regeneration, while modifications of the implant surface by incorporation of biologic mediators of growth and differentiation may be potentially beneficial in enhancing wound healing following implant placement.

Balaram Naik et al (2013)[22], conclude that PRF first described by Choukroun is a new second generation of platelet concentrate. Simplified processing technique without any complex handling makes it superior to PRP. PRF can be used to promote wound healing, bone regeneration, graft stabilization, wound sealing, and hemostasis. Because the fibrin matrix is better organized, it is able to more efficiently direct stem cell migration and the healing program. Release of growth factors from PRF through in vitro studies and good results from in vivo studies led to optimize the clinical application of PRF. It was shown that there are better results of PRF over PRP. Dohan proved a slower release of growth factors from PRF than PRP and observed better healing properties with PRF. It was observed and shown that the cells are able to migrate from fibrin scaffold, while some others demonstrated the PRF as a supportive matrix for bone morphogenetic protein as well.

Banerjee Nandini et al (2013)[2], concluded that the placement of implants and their immediate restoration whether provisional or final can be highly advantageous. However care and appropriate surgical and prosthetic considerations need to be highly contemplated when performing these procedures. Its success rate may differ slightly from completing procedures in a more conventional way. One of the greatest and most advantageous application of immediate restoration of implants are those cases in which esthetic needs and soft tissue preservation are most important. This review discusses the different aspects of dental implant including its advantages over the

contemporary dental removable implants and its procedures in detail. It also has a small consideration on mini dental implants.

Manish Goutham et al (2013)[6], concluded that success in implant dentistry depends on several parameters that may improve considering both biologic and mechanical criteria. To explain the micro mechanisms involved in osseointegration it is necessary to know concepts of biology, physiology, anatomy, surgery and tissue regeneration. This means that osseointegration should be regarded not as an exclusive reaction to specific implant material but as the expression on the endogenous basic regenerative potential of bone. Bioactive materials bond to bone tissue through bridges of calcium and phosphorus. On the other hand, the chemical bond between non coated titanium implants and living tissue occurs through weak Van der waals and hydrogen bonds. Use of laser and bioactive molecule gives a broad scope for researchers and more studies are needed to improve osseointegration more efficiently.

Renu kundu, et al (2014)[1], found that stability of implants was high on the day of placement. Marked decrease in implant stability was noticed at one month based on periotest values compared to baseline. Comparison with PRP and non-PRP groups, showed a statistically significant difference in implant stability with PRP at baseline. The effect of PRP on bone height changes was not statistically significant. A synergistic effect of PRP and square thread-form was observed on improved implant stability and bone levels, however, no such effect is

seen with PRP and reverse buttress thread-form. Short follow up period, assessment of bone in one direction i.e., height were some of the limitations of the study.

Dr.Shikha et al (2014)[3], concluded that osseointegration of dental implants is the process of bone growing right up to the implant surface. No soft tissue connects the bone to the surface of the implant. No scar tissue, cartilage or ligament fibers are present between the bones and implant surface. The direct contact of bone and implant surface can be verified microscopically. When osseointegration occurs, the implant is tightly held in place by the bone. The process typically takes four to six months to occur well enough for the implant dentist to complete the restorations and also stated that osseointegration is a multifactorial entity. It is because of the attention to training, research and clinical studies that osseointegration has now become an accepted part of the treatment regime in many countries worldwide and no longer regarded as the last resort when all else has failed but often as a treatment of choice.

Dr.Gilsa Vasunni et al (2014)[27], concluded that flapless surgery can be done either by punching a small amount of soft tissue or directly drilling through the soft tissue. Avoiding the mucoperiosteal flap results in less bleeding, postoperative swelling and discomfort. The second stage surgery requires less adjustment for healing abutment placement. Moreover since the periosteum is not reflected, it maintains better blood supply to the site reducing the amount of bone resorption.

In addition flapless surgery maintains the soft tissue architecture and decreases the operating time. The study showed that on the mesial side the mean change from month 0-1, month 1-3, month 3-6 and month 0-6 for flapless technique was significantly lower than with flap technique, similarly on distal side mean change from month 0-1, month 1-3, month 3-6 and month 0-6 for flapless technique was significantly lower than with flap technique . This shows that loss of bone during the 6 months period on the mesial and distal side of the implant placed with flapless method was significantly lower compared to those placed using with flap method.

Anshul Chugh et al (2014)[31], concluded that Crestal bone loss around dental implants is considered to be one of the major problems and its preservation around implant is the key to long-term success of an implant restoration. The amount of crestal bone lost during the first year of implant service affects the longevity of the implant. Various causes of greater crestal bone loss in the first year of implant function are surgical trauma, occlusal overload, peri-implantitis, presence of microgap, reformation of biologic width and implant crest module design. The study was undertaken to observe the amount of crestal bone loss, occurring at the end of 6 months after placing the implants and before loading it prosthetically. According to the established criteria for the assessment of implant survival and success, marginal bone level change in first year should be less than 1.5 mm.

Sinisia Mirkovic et al (2015)[29], found that coagulation and blood clot formation in bone defects is sometimes followed by retraction of a blood clot and serum extrusion, thus producing peripheral serum-filled spaces between bony wall and coagulum. This can result in a higher incidence of postoperative complications. Stabilization of blood coagulum, which enables successful primary healing, may be accomplished by autotransplantation, allotransplantation, xenotransplantation or application of autologous platelet concentrate and concentrated growth factors (CGF). Application of fibrin rich blocks containing CGF is one of the possible methods for reconstruction of bone defects. CGF can be applied alone or mixed with a bone graft. The method is relatively simple, without risk of transmissible and allergic diseases and economically feasible. Also CGF is efficient in significant shortening of bone healing time particularly in massive bone defects reducing the incidence of post operative relapse, enabling better restitution of surrounding soft tissue structures.

Tejesh Yelamali et al (2015)[15], concluded that PRF is significantly better in promoting soft tissue healing and also faster regeneration of bone after third molar extraction, in comparison with PRP. Although, both PRF and PRP clinically showed very good soft tissue healing as measured by healing index of Landry et al., further studies with larger sample size are needed to show much convincing effects of these biomaterials in terms of soft tissue healing. Moreover, PRF definitely showed to promote better osseous regeneration over PRP

in terms of uniformity and density of regenerated bone which is statistically significant. Although, the present study was done with a four month follow-up and the osseous regeneration was only measured indirectly over computer aided software (Adobe Photoshop CS), PRF did attribute to be a much simpler and a better platelet concentrate, in promoting soft tissue healing and osseous regeneration over PRP.

Peter mansour et al (2015)[26], concluded that during normal wound healing, the fibrin matrix is important in haemostasis, however more crucial is its role in acting as the initial scaffold for the new extracellular matrix. It allows binding of cells and healing proteins to the scaffold, such as platelets, WBCs, fibroblasts and osteoblasts, endothelial cells and smooth muscle cells. Fibrin has also been shown in animal models to be an important determinant of angiogenesis, as fibrin deposited in subcutaneous tissue induces angiogenesis. Furthermore, many studies have shown that wound healing is largely dictated by fibrin structure, in density, number of branch points, porosity and permeability. The fibrin physical structures are determined by many factors including clotting rate, Factor XIII concentration, thrombin, chloride ions, pH, etc.

MATERIALS AND METHODS

IRB Approval:

Before the start of the study, the methodology was presented to the IRB and approval was obtained.

IRB/IEC Reference No: 2014-MD-Brl-VEN-02

Sampling procedure	Random selection of population (Sealed envelope method)
No. of Groups	Two Control group (Group 1) & Experimental group (Group 2)
Sample size	20

Patient Selection:

Patients were selected by means of volunteers recruitment process. Patients interested in replacing missing teeth with dental implants were selected.

Inclusion Criteria:

- Subjects with missing teeth indicated for implant therapy
- Physically healthy individuals (ASA I/II) indicated for implant therapy
- Selected Subjects who had given signed informed consent. (Fig 7)

Exclusion Criteria:

- All contraindicated patients for implant therapy
- Medically compromised individuals

- Subjects with medication known to interfere with wound and bone healing.

Sealed Envelope Randomization:

The participating patients were given randomly generated treatment allocations within sealed opaque envelopes. Once a patient has consented to enter a trial, an envelope is opened and the patient is then offered the allocated treatment regimen.

Surgical Phase:

The Osseoset physiodispenser (Nobel biocare) with 20:1 W & H Reduction Gear Hand piece was used for Osteotomy preparation. Osteotomy preparation was done following standard surgical protocols with copious internal and external irrigation as follows:

a) Mandibular arch – 800 RPM/20 µm Torque
b) Maxillary arch – 700 RPM/20 µm Torque

For control group (Group 1) 10 implants (Nobel biocare) (Fig 8) were placed following standard surgical protocol. For experimental group (Group 2), 10 implants (Nobel biocare) were placed following standard surgical protocol augmented with concentrated growth factor (CGF) (Fig 5). Among 20 implants, 12 implants (6 coated with CGF) were placed in maxilla and 8 implants (4 coated with CGF) were placed in mandible.

Implant Placement Protocol: (Control)

Osteotomy preparation was done following standard surgical protocols with adequate irrigation. For this group, implants were placed without CGF. (Fig 9)

Implant Placement Protocol: (Experimental)

Osteotomy preparation was done following standard surgical protocols with adequate irrigation. For this group, implants were placed with CGF by coating around the implants and in the prepared socket. (Fig 9)

C.G.F Production Technique:

C.G.F is produced by collecting the patient's blood into 10ml test tubes (Fig 3), which are immediately centrifuged with the Medifuge silfradent centrifuge (Fig 1&2). Up to 8 test tubes can be taken at any one time, with no need to add any other substances, and a single centrifugation will yield 3 fractions in each test tube. A lower part with the red globules, a higher part containing cell plasma (PPP) and at the centre of the two fractions, we have a coagulation of fibrin that will be taken from the test tube and separated from the red fraction with scissors. The coagulation may be used in the form of a membrane, by compressing it, or in fragments created by fragmenting the coagulation itself. (Fig 4)

Once filled, the test tubes are quickly placed into the rotor of the Medifuge (Silfradent, Italy) (Fig1&2) centrifuge accelerator, without shaking them. This has elite distinctiveness with regards to:

- characteristics and mechanical structures, such as the monolithic sterilisable rotor
- calibrated angled test tube
- working temperature
- rotation chamber disinfection
- dynamic characteristics
- settings: start, acceleration, speed
- brake for the fluid to be centrifuged and
- automatic, closed lid disinfection.[26]

All this features enable us to obtain more greatly differentiated components from the test tube. After approximately 13 minutes of rotation, the serum is separated from the other phases of the CGF and stored in a precise sterile dappen dish. The fibrin phase is separated and stored in diluted antibiotic solution. The initial portion of the coagulation containing the GFs and the stem cells are immediately stored in the dappen provided. The coagulum, which is rich in red blood cells and platelets, as well as iron, calcium and other fundamental components, is prepared to be used for the preparation of fillers, for mixtures of biomaterials or autologous bone taken for osteotomy.[26]

The fibrin block, separated from the red phase, is prepared to be shifted according to the clinical need: direct cavity graft, shaped membrane with the use of the specific forceps provided, graft particle to be mixed with biomaterial or living autologous bone.[26]

Implant Placement Procedure:

Prior to surgery, careful and detailed planning was done to identify vital structures such as the inferior alveolar nerve or the sinus as well as the bone shape and dimensions to properly orient the implants for the most predictable outcome. Two-dimensional radiographs, such as orthopantomographs and periapical radiographs were made prior to the surgery. The placement of a dental implant requires preparation of the bone using precision drills supplied by the Nobel biocare Implant surgical kit with highly regulated speed and torque as prescribed previously in the surgical phase was done to prevent overheating or putting too much pressure on the bone. (Fig 6)

Healing Time:

In general, implants are normally allowed to heal for 2–6 months before they are used to support bridges, crowns or dentures. Studies have shown that early loading of implant may not increase early or long term complications. But, if the implant is loaded too soon, it is possible that the implant may move which finally results in failure. Therefore it is imperative for patient to follow post operative instructions strictly to maximize implant success. (Fig 10)

Post Surgical and Recall Level Radiographs:

Orthopantamogram and Intra oral periapical radiographs using RVG (radiovisiography) were taken after each implant placement. Orthopantamogram and radiographs were taken at the baseline, after first, third and sixth month.

Data Collection Phase:

The peri-implant bone density and crestal bone levels around implants were measured at 0, 1st, 3rd & 6th month after implant placement.

Analysis of Crestal Bone Level:

The crestal bone levels were assessed using digitalized Orthopantamogram (Signora) (Fig 11&12). The top surface of the implant was used as the reference line and the first bone- implant contact on mesial and distal aspect was used as the bone level indicator.[27] Perpendicular lines were dropped from the reference line and the bone level on the mesial and distal sides of the implant and the distance was measured to the nearest 0.01 mm with the image tool (Signora). The readings were recorded at baseline, one month, three months and six months for all groups. All measurements were performed by an instructed dental student and checked by another investigator under supervision of the main investigator of the study. The mean bone loss was calculated. These readings were then analysed statistically.

Analysis of Bone Density:

The peri-implant bone density was assessed by Digora software (Fig 13). Digora software has increased sensitivity in the detection of bone changes non-invasively. Four digitalized OPG are taken at pre-scheduled intervals. Nine points were marked around implants (Mesially four points, distally four points and apically one point). Mesial four points M1, M2, M3, M4 were placed in the precise positions between thread no.2 and 3, 4 and 5, 6 and 7 and 8 and 9 of the implant on the mesial aspect and Distal four points D1, D2, D3, D4 were placed in similar points on the distal aspect and point A was marked 1 mm apically from the apex of the implant. The images were compared at different intervals using Digora Software.[28] The radiographic density differences between each interval were evaluated and analysed.

Fig 1: Medifuge Centrifuge

Fig 2: Medifuge Centrifuge – Top View

Fig 3: Withdrawing Blood For CGF

Fig 4: Blood Sample After Centrifugation

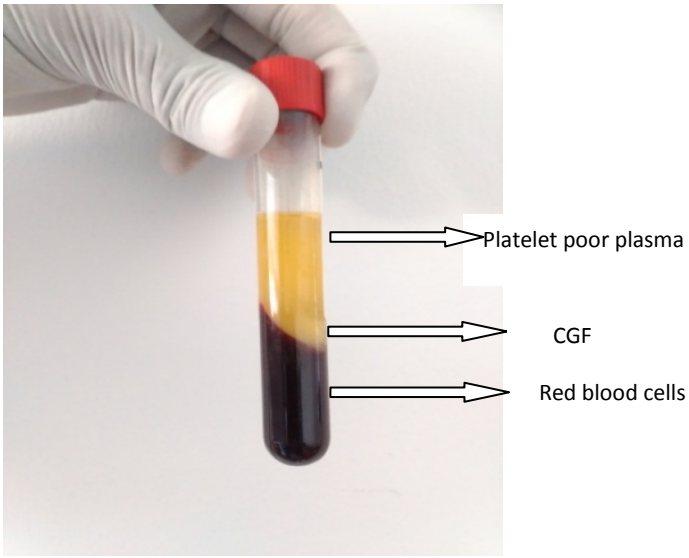


Fig 5: Concentrated Growth Factor

Fig 6: Implant Placement Armamentarium

Fig 7: Implant Patient

Fig 8: Replace select tapered Implant (Nobel Biocare)

Fig 9: Implant Placement Procedure

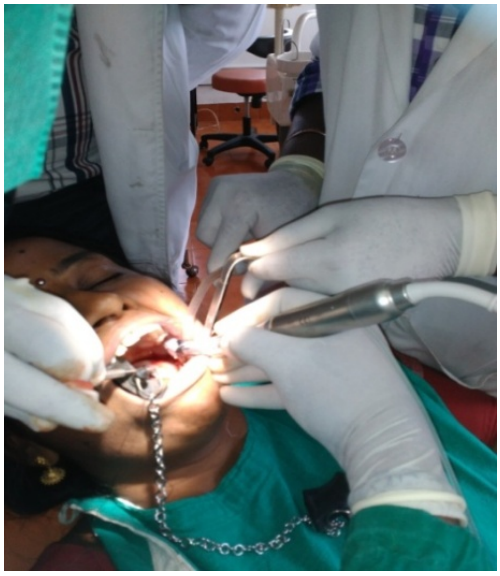


Fig 10: After Implant Placement

Fig 11: Measurement of Crestal Bone - Mandible

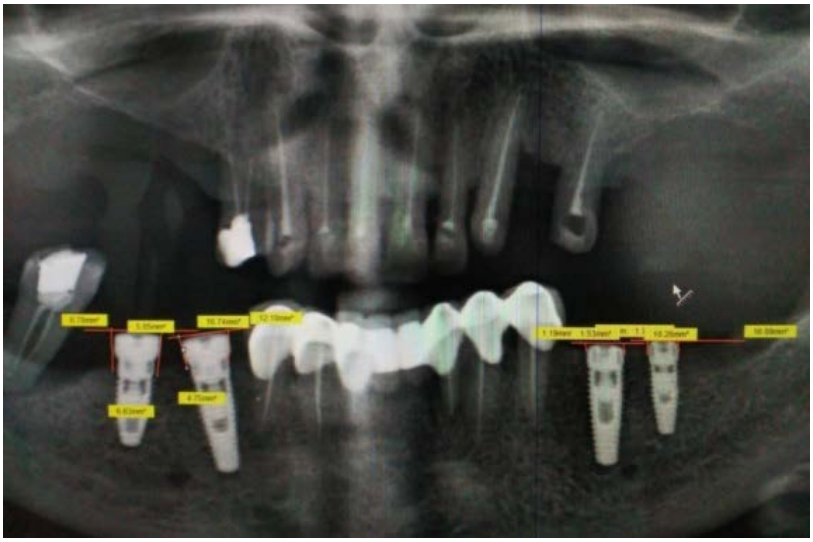


Fig 12: Measurement of Crestal Bone - Maxilla

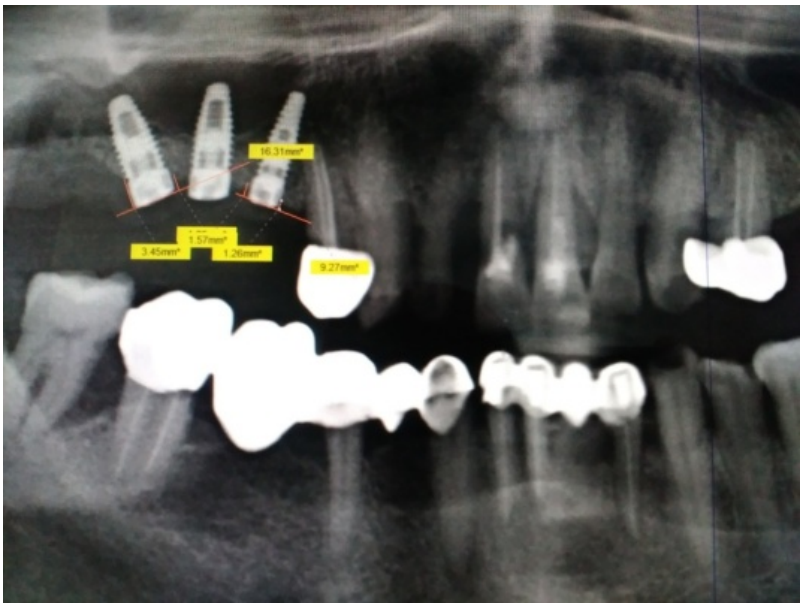
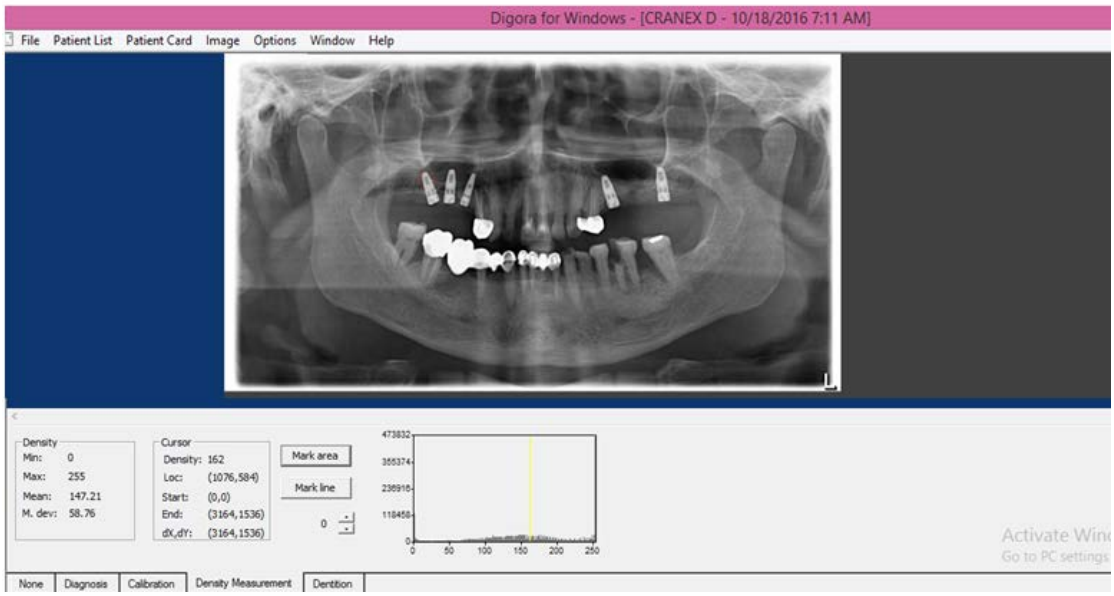


Fig 13: Measurement Of Bone Density By Digora Software



RESULTS

Out of the twenty implants which were placed for the study, 10 implants (50%) were placed without concentrated growth factors (Group 1) and 10 implants were placed with concentrated growth factors (Group 2). The results were tabulated and statistically analysed.

Intergroup comparison (Group 1 – without CGF, Group 2 – with CGF) of mean bone level for Group 1 from mesial baseline to 1st month, 3rd and 6th month were 0.120, 0.213 & 0.345 respectively., and Group 2 at 1st, 3rd and 6th month were 0.074, 0.171 & 0.294 respectively., (Table 3). Mean bone level for Group 1 from distal baseline to 1st month, 3rd and 6th month were 0.133, 0.248 & 0.331 respectively and Group 2 at 1st, 3rd and 6th month were 0.100, 0.222 & 0.320 respectively (Table 3). On analyzing the results statistically, there was not significant difference between the two groups (Table 4). Intragroup comparison in Group 1 and Group 2 were also not statistically significant (Table 4). Differences in the crestal bone levels were not statistically significant at all the time intervals (From baseline to 1st month, 3rd month and 6th month) (Table 1&2).

Intragroup comparison of mean bone density in Group 1 at baseline, 1st month, 3rd month and 6th month were 0.60, 1.10 & 1.10 and in Group 2 it were 2.60, 5.70 & 5.7 respectively., (Table 7). In Group 1 the difference between baseline and 1st month, baseline and 3rd month and baseline and 6th month were 0.6, 1.1, & 1.1 respectively and for Group 2 it was 2.6, 5.7, 5.7 respectively (Table 7 & 8). On

analyzing the results statistically, there was a statistically significant difference between baseline and 1st month, baseline and 3rd month and base line and 6th month in Group 2, but in Group 1, the differences were not statistically significant (Table 9). Intergroup comparison of mean bone density values between two groups Group 1 and Group 2 were statistically significant. (Table 8 & 9)

STATISTICAL ANALYSIS:

In this study, Student t-test (paired and unpaired) was used. Paired t-test was used to measure at two different points from the data collected from subjects whereas unpaired t-test was used to measure from two different and independent subjects. Paired and unpaired t-tests were used to evaluate the intra and inter-group differences in bone density around implants and unpaired t-test was used to compare the differences between two groups in crestal bone levels. The values of peri-implant bone density was compared with baseline at one month, at three months and at six months within same group and between groups and crestal bone level values was compared at baseline, one month, three months and six months between groups. The readings obtained were analysed by SPSS Software (Version 19.0). The p-value was taken significant at $p< 0.05$ and highly significant at $p< 0.01$.

ASSESSMENT AND COMPARISON OF CRESTAL BONE LEVELS BETWEEN THE GROUPS.

TABLE 1: CRESTAL BONE VALUES AND DIFFERENCES AT BASELINE, 1ST, 3RD & 6TH MONTH (WITHOUT CGF)

Implant without CGF (Group 1) (readings in mm)													
Baseline reading		At 1st month		At 3rd month		At 6th month		Diff btwn baseline and 1st month		Diff btwn baseline and 3rd month		Diff btwn baseline and 6th month	
Mesial	Distal	Mesial	Distal	Mesial	Distal	Mesial	Distal	Mesial	Distal	Mesial	Distal	Mesial	Distal
1.19	1.53	1.24	1.61	1.31	1.68	1.42	1.72	0.05	0.08	0.12	0.15	0.23	0.19
2.05	1.73	2.16	1.81	2.21	1.92	2.28	1.99	0.11	0.08	0.16	0.19	0.23	0.26
3.09	3.02	3.14	3.14	3.21	3.19	3.32	3.21	0.05	0.12	0.12	0.17	0.23	0.19
1.5	2.83	1.78	2.91	2.04	3	2.33	3.06	0.28	0.08	0.54	0.17	0.83	0.23
2.98	2.97	3.02	3.35	3.08	3.35	3.13	3.43	0.04	0.38	0.1	0.38	0.15	0.46
0.82	1.23	0.98	1.34	1	1.44	1.21	1.54	0.16	0.11	0.18	0.21	0.39	0.31
0.76	2.27	0.98	2.33	1.1	2.42	1.21	2.51	0.22	0.06	0.34	0.15	0.45	0.24
2.19	2.51	2.28	2.56	2.32	2.62	2.49	2.76	0.09	0.04	0.13	0.11	0.3	0.25
2.17	1.26	2.31	1.42	2.44	1.52	2.63	1.57	0.14	0.16	0.27	0.26	0.46	0.31
1.78	2.59	1.84	2.81	1.95	3.28	1.96	3.46	0.06	0.22	0.17	0.69	0.18	0.87

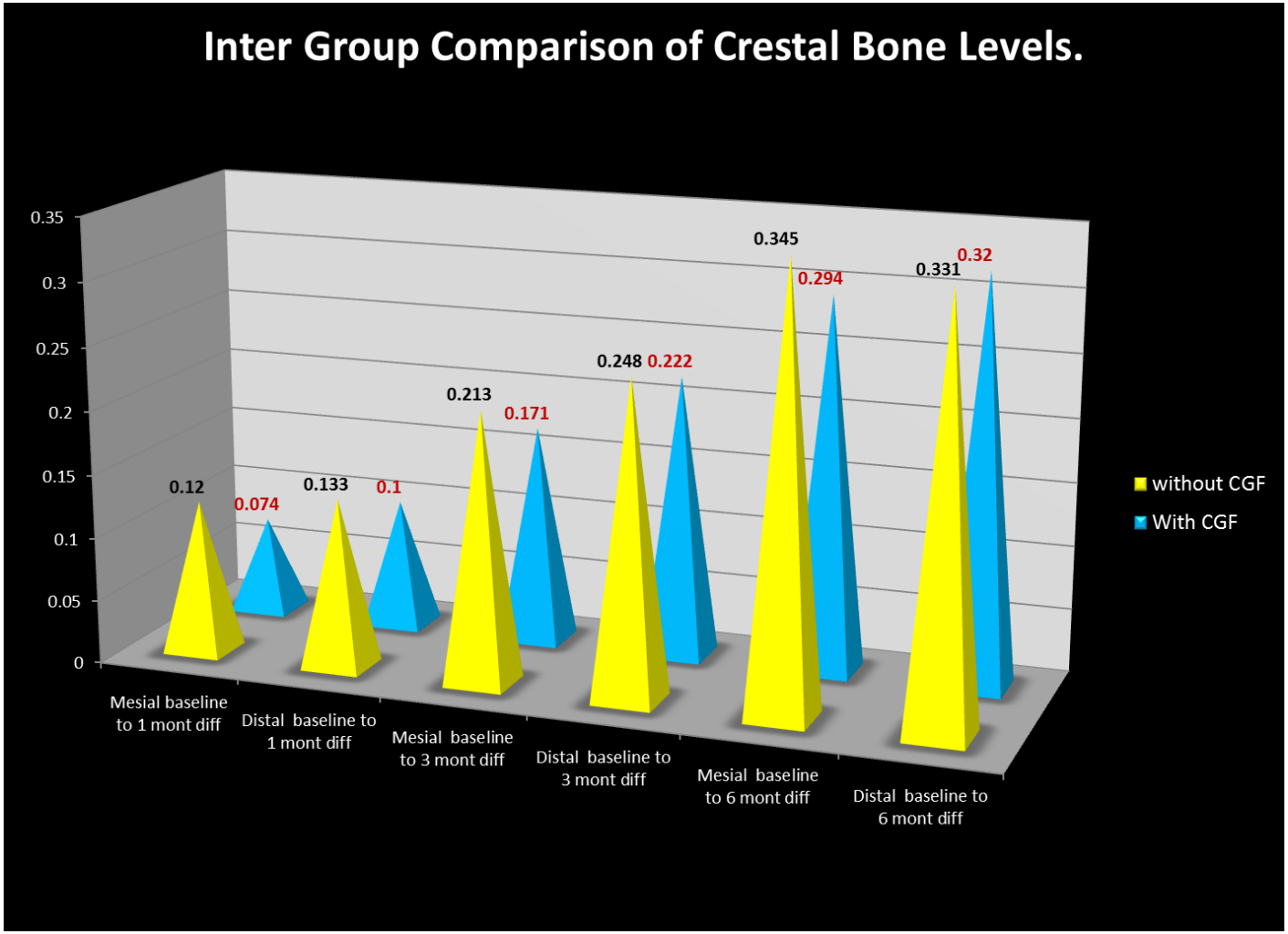
TABLE 2: CRESTAL BONE VALUES AND DIFFERENCES AT BASELINE, 1ST, 3RD& 6TH MONTH (WITH CGF)

Implant with CGF (Group 2) (readings in mm)													
Baseline reading		At 1st month		At 3rd month		At 6th month		Diff btwn baseline and 1st month		Diff btwn baseline and 3rd month		Diff btwn baseline and 6th month	
Mesial	Distal	Mesial	Distal	Mesial	Distal	Mesial	Distal	Mesial	Distal	Mesial	Distal	Mesial	Distal
4.19	4.72	4.21	4.82	4.32	4.84	4.46	4.86	0.02	0.1	0.13	0.12	0.27	0.14
4.34	3.72	4.42	3.81	4.51	3.94	4.62	3.96	0.08	0.09	0.17	0.22	0.28	0.24
3.46	3.24	3.52	3.34	3.61	3.52	3.84	3.56	0.06	0.1	0.15	0.28	0.38	0.32
1.26	1.57	1.31	1.68	1.34	1.71	1.38	1.73	0.05	0.11	0.08	0.14	0.12	0.26
1.95	3.45	1.98	3.54	2.19	3.67	2.5	3.69	0.03	0.09	0.24	0.22	0.55	0.24
1.5	2.04	1.62	2.15	1.74	2.29	1.84	2.34	0.12	0.11	0.24	0.25	0.34	0.3
1.4	0.66	1.52	0.76	1.62	0.98	1.73	1.06	0.12	0.1	0.22	0.32	0.33	0.4
1.1	1	1.13	1.1	1.21	1.31	1.37	1.37	0.03	0.1	0.11	0.31	0.27	0.37
1.22	2.59	1.34	2.68	1.37	3.02	1.39	3.16	0.12	0.09	0.15	0.03	0.17	0.57
3.25	2.16	3.36	2.27	3.47	2.49	3.48	2.52	0.11	0.11	0.22	0.33	0.23	0.36

TABLE 3: INTER GROUP COMPARISON OF CRESTAL BONE VALUES

	Groups	N	Mean	Std. Deviation	Mean difference	p value
Mesial baseline to 1 mont diff	without CGF	10	.120	.081	.046	.13
	With CGF	10	.074	.041		
Distal baseline to 1 mont diff	without CGF	10	.133	.101	.033	.32
	With CGF	10	.100	.008		
Mesial baseline to 3 mont diff	without CGF	10	.213	.137	.042	.38
	With CGF	10	.171	.057		
Distal baseline to 3 mont diff	without CGF	10	.248	.173	.026	.68
	With CGF	10	.222	.098		
Mesial baseline to 6 mont diff	without CGF	10	.345	.202	.051	.50
	With CGF	10	.294	.119		
Distal baseline to 6 mont diff	without CGF	10	.331	.205	.011	.88
	With CGF	10	.320	.117		
*Unpaired t test						

TABLE 4: COMPARISON OF MESIAL & DISTAL BASELINE TO 1ST, 3RD& 6TH MONTH (GROUP 1 &2)



ASSESSMENT AND COMPARISON OF BONE DENSITIES

TABLE 5: BONE DENSITY VALUES WITHOUT CGF (READINGS AT BASELINE, 1ST MONTH, 3RD & 6TH MONTH)

without CGF						
Baseline reading	At 1st month	At 3rd month	At 6th month	Diff btwn baseline and 1st month	Diff btwn baseline and 3rd month	Diff btwn baseline and 6th month
198	199	200	200	1	2	2
200	201	202	202	1	2	2
206	205	205	205	-1	-1	-1
162	162	163	163	0	1	1
161	162	163	163	1	2	2
164	165	166	166	1	2	2
160	161	160	160	1	0	0
192	193	192	192	1	0	0
182	183	184	184	1	2	2
184	184	185	185	0	1	1

TABLE 6: BONE DENSITY VALUES WITH CGF (READINGS AT BASELINE, 1ST MONTH, 3RD & 6TH MONTH)

With CGF						
Baseline reading	At 1st month	At 3rd month	At 6th month	Diff btwn baseline and 1st month	Diff btwn baseline and 3rd month	Diff btwn baseline and 6th month
198	201	204	204	3	6	6
196	199	202	202	3	6	6
200	202	205	205	2	5	5
161	163	166	166	2	5	5
162	165	168	168	3	6	6
160	162	165	165	2	5	5
162	165	168	168	3	6	6
192	195	198	198	3	6	6
182	185	188	188	3	6	6
183	185	189	189	2	6	6

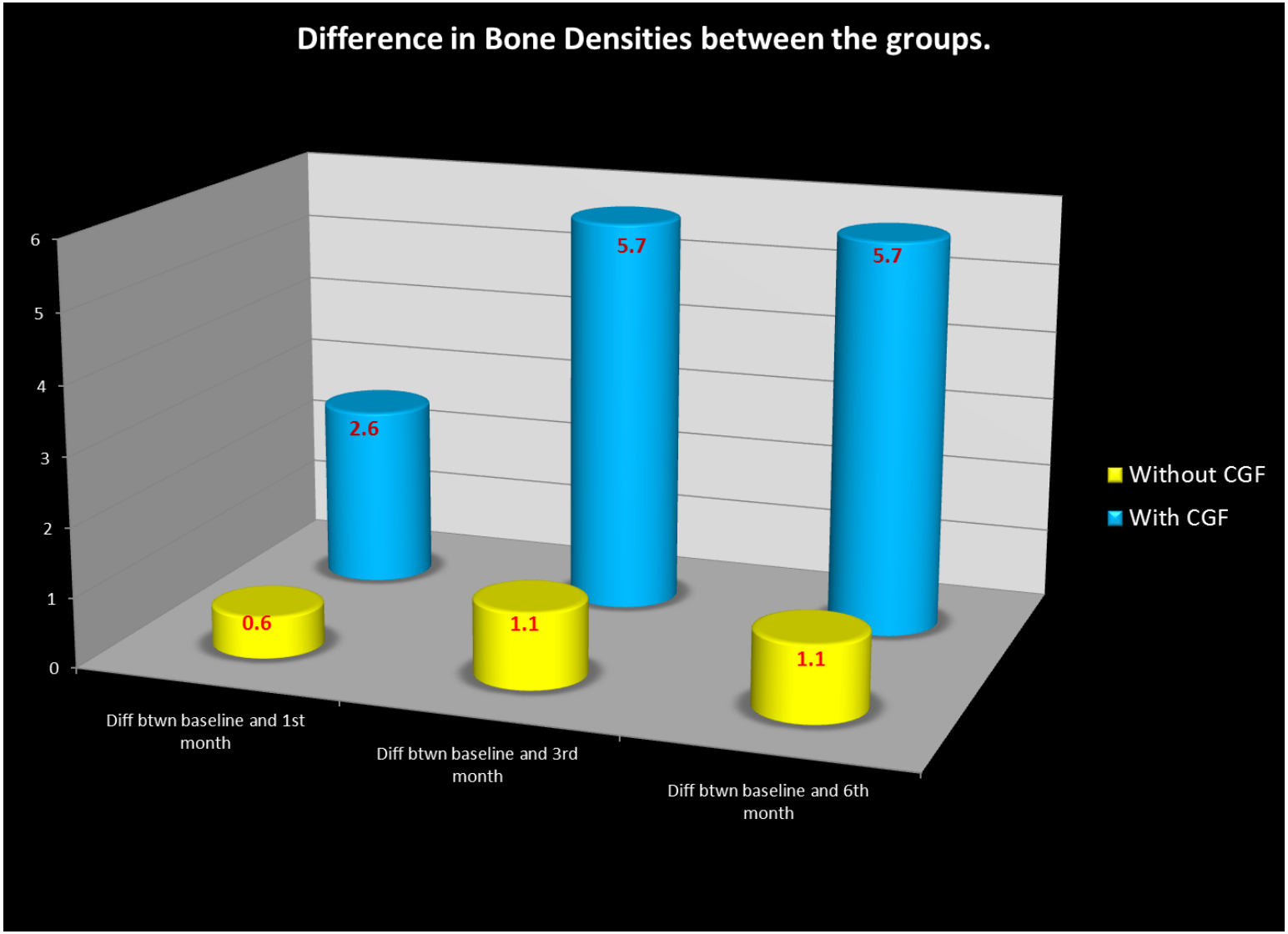
TABLE 7: INTRA GROUP COMPARISON OF BONE DENSITY (WITH & WITHOUT CGF)

Paired Samples Statistics							
Group			N	Mean	Std. Deviation	Mean difference	p value
1	Pair 1	Baseline reading	10	180.9	17.94	0.6	0.02
		at 1st month	10	181.5	17.74		
	Pair 2	Baseline reading	10	180.9	17.94	1.1	0.01
		at 3rd month	10	182	17.73		
	Pair 3	Baseline reading	10	180.9	17.94	1.1	0.01
		at 6th month	10	182	17.73		
2	Pair 1	Baseline reading	10	179.6	16.81	2.6	<0.001
		at 1st month	10	182.2	16.92		
	Pair 2	Baseline reading	10	179.6	16.81	5.7	<0.001
		at 3rd month	10	185.3	16.94		
	Pair 3	Baseline reading	10	179.6	16.81	5.7	<0.001
		at 6th month	10	185.3	16.94		

TABLE 8: INTER GROUP COMPARISON OF BONE DENSITY (WITH & WITHOUT CGF)

Bone density - Between group comparison						
	Group	N	Mean	Std. Deviation	Mean diff	p value
Diff btwn baseline and 1st month	1	10	0.6	0.7	2	<0.001
	2	10	2.6	0.52		
Diff btwn baseline and 3rd month	1	10	1.1	1.1	4.6	<0.001
	2	10	5.7	0.48		
Diff btwn baseline and 6th month	1	10	1.1	1.1	4.6	<0.001
	2	10	5.7	0.48		

TABLE 9:COMPARATIVE ANALYSIS OF BONE DENSITY FROM BASELINE TO 1ST, 3RD&6TH MONTH (GROUP 1& 2)



DISCUSSION

From 1990's, till today growth factors have emerged as the "Holy Grail" in wound healing.[15] Researches by Dong-seok sohn and others showed that concentrated growth factors (CGF) improve bone formation and plays a vital role in osseointegration of implants. Growth factors play a major role to repair or generate tissues. Most of the growth factors are in blood plasma and platelets. So platelet concentrates contains sufficient growth factors such as platelet derived growth factors (PDGF), Transforming growth factors (TGF- β), Insulin like growth factors (IGF- I), Epidermal growth factors (EGF), Vascular Endothelial Growth Factors (VEGF), basic Fibroblast Growth Factors (bFGF).[25]

Concentrated growth factors is known to have higher tensile strength, higher concentration of growth factors and higher resistance to flow than Platelet rich fibrin (PRF), Platelet rich plasma (PRP) and hence compressed CGF can be used as barrier membrane with growth factors as alternative collagen membrane. This barrier membrane induces faster formation and fast tissue healing.[25]

CGF & ITS IMPORTANCE

Concentrated growth factors CGF (Fig 5) is well known to accelerate new bone formation. Other blood derivatives like Platelet rich Plasma uses complex protocols to prepare and chemical additives. Concentrated growth factor, overcomes these disadvantages. CGF does not require any chemical or allergenic additives such as Bovine

thrombin or anticoagulants, so is free from viral transmission diseases. CGF is 100 % autologous fibrin.[24] CGF can be used alone or with a bone graft.[29] CGF with fibrin rich blocks induce fast new bone formation.[30]

Fabrication of CGF:

The calibrated centrifugation carried out with the Medifuge phase separator (Silfradent, Italy). The apparatus accurately designed so as to guarantee the maximum exploitation of the blood's potential by controlling the Speed, Time, Temperature, acceleration and controlled speed and Gravitational acceleration of approximately RCF200. The development and growth of the fibrin gel block during the centrifugation and specially during the polymerisation, allows for a volume growth of the chains in all directions.[26] CGF, like PRF, does not require the inclusion of bovine thrombin or any anticoagulants. Additionally, altered protocols in receiving the blood sample and in the centrifuging procedure compare with PRF. Unlike PRF however, CGF uses variable rpm from 2400-2700 to separate cells in the venous blood, which results in fibrin rich blocks that are larger, denser and more affluent in growth factors than common PRF. This shows enhanced regenerative capacity and superior versatility when using the fibrin rich block.[26]

The CGF is characterised by four phases:

1. A superior phase represented by the serum (blood plasma in absence of fibrinogen and coagulation factors).

2. An interim phase represented by a very huge and dense polymerised fibrin block.

3. A liquid phase containing the Growth Factors, white line cells and stem cells waiting for stimulation and to differentiate into specialized cell types.

4. A lower red portion consists of a viscous, dense, platelet-rich coagulation.[26]

The phases and their components are:

1. Serum

Serum is the lightest and most liquid part of blood. It is fibrinogen-free and has only a few cells. It should be kept cool and mixed quickly to avoid denaturing the proteins.[26]

It is a clear and straw yellow in colour and consists of:

- 92% Water
- 7% proteins, mineral salts, Carbondioxide
- Proteins: albumin and antibodies
- Nutrients: glucides, amino acids, lipids and enzymes
- Hormones
- Inorganic electrolytes

2. Fibrin Buffy Coat

The polymerized fibrinogen molecules (FG), the resultant fibrin block comprises three-dimensional polymer networks with interwoven fibres, all collected in a single phase in the form of a gel in a single phase. During polymerisation, the fibres grow in diameter.[26]

3. The Growth Factors and the unipotent Stem Cells

Below the buffy coat and above the dense clot portion lies the growth factors and unipotent stem cells. This phase can be aspirated with a pipette and mixed with autologous bone to obtain an extremely high performance activated graft.[26]

4. Coagulum:

In the CGF technique, the red phase consists of concentrated red and white blood cells, platelets and clotting factors. It appears like a dark reddish dense gel, and can be used in its pure form or added with fibrin particles and/or autologous or heterologous bone when filling very enormous defective areas.[26]

CGF in regenerative surgery should therefore be considered as a multifactorial stimulation system. This versatility and multiplicity of applications makes it successful from all the other techniques proposed so far.[26]

Mode of action of CGF:

The ensuing fibrin clot or block is of a greater quality due to the concentration of factor XIII, fibrinogen and thrombin that is obtained. Factor XIIIa, which is activated by thrombin, cross links the fibrin clot to increase stability, strength and protection against plasmin mediated degradation. Clinically, this results in a clot with higher tensile strength, adhesive strength, and decline in haemostatic time (105 secs vs 360 secs).[26]

Besides the tensile fibrin membrane, a red phase of concentrated red blood cells and platelets are obtained. This is often mixed with either autogenous or other fillers for a more easy to handle and voluminous cavity filling method. In actual fact the CGF is an upgraded version of PRF with a strengthened fibrin matrix and boosted growth factors and cytokines.[26] During normal wound healing, the fibrin matrix is essential in arrest of bleeding, however more crucial is its role in acting as the initial scaffold for the new extracellular matrix. It allows mixing of cells and healing proteins to the scaffold, such as platelets, White blood corpuscles, fibroblasts and osteoblasts, endothelial cells, and smooth muscle cells.[26]

Keratinocytes bind to fibrin. By expressing sites for binding of cytokine, growth factors and adhesion molecules for cells, wound healing was indirectly promoted by fibrins. Fibrin has also been shown in animal models to be an important determinant of angiogenesis, as fibrin deposited in subcutaneous tissue initiates angiogenesis.[26]

In addition, studies have shown that wound healing is largely dictated by fibrin structure; in density, porosity, number of branch points and permeability. The fibrin physical structures are determined by many factors including clotting rate, Factor XIII concentration, chloride ions, pH and thrombin etc. Optimizing these conditions is part of the aim of the CGF protocol.[26]

Pathological alterations of these fibrin fibers occur in diseases like diabetes and this clearly leads to disturbances in wound healing process. Thus these are the patients that are most likely to benefit from CGF.[26]

Further to the fact that CGF not only uses an autogenous source of growth factors and membrane, there are no added derived products of animals as in PRP. With no anticoagulants added, the platelets begin to be activated naturally alongside the coagulation cascade. The resulting matrix or membrane rich in fibrin works synergistically with these growth factors.[26]

CRESTAL BONE LEVELS & PERI-IMPLANT BONE DENSITY

Crestal bone loss around dental implants is considered to be one of the most important problems and its maintenance around implant is very vital for long-term triumph of an implant restitution. The amount of crestal bone lost during the first year after the implant placement affects the implant longevity. Surgical trauma, peri-implantitis, occlusal overload, microgaps, biological width and crest module of implant are various causes of crestal bone loss. This present study was

undertaken to observe the amount of crestal bone level differences at the end of first month, third and sixth months among implants placed with and without the presence of Concentrated growth factors. According to the established criteria for the assessment of implant survival and success, in the first year the marginal bone level change should be less than 1.5 mm. Smith and Zarb concluded that alveolar bone loss should be less than 0.2 mm is one of the criteria for implant success.[31]

In this study, Intergroup comparison (Group 1 - without CGF, Group 2 - with CGF) of mean crestal bone level for Group 1 from mesial baseline to 1st month, 3rd and 6th month were 0.120, 0.213 & 0.345 respectively., and Group 2 at 1st, 3rd and 6th month were 0.074, 0.171 & 0.294 respectively., (Table 3). Mean bone level for Group 1 from distal baseline to 1st month , 3rd and 6th month were 0.133, 0.248 & 0.331 respectively., and Group 2 at 1st, 3rd and 6th month were 0.100, 0.222 & 0.320 respectively (Table 3). On analyzing the results statistically, there was not significant difference between the two groups (Table 4). Intragroup comparison in Group 1 and Group 2 were not statistically significant (Table 4). Differences in the crestal bone levels were not statistically significant at all the time intervals (From baseline to 1st month, 3rd month and 6th month) (Table 1&2). Though the difference is within the success criteria of implant (mean crestal bone loss < 1.5mm in one year), there is not much significant differences on mesial and distal aspects around implants between two groups (Table 3& 4). These results were in accordance with the pilot

study done by Anshul Chugh et al., on radiological evaluation of marginal bone around dental implants.[31]

Another part of study was done to analyse the effect of Concentrated growth factors on peri-implant bone denstiy. A total of 20 implants placed with and without concentrated growth factors and difference in the bone density values were analysed from baseline to one month, three months and six months .

Intragroup comparison of bone density values without CGF (Group 1) shows the mean difference from baseline to one month is 0.6, and after three and six months periods are 1.1 and 1.1 respectively which indicates not much significant improvement in bone density values without concentrated growth factors. On the other hand, mean difference of the bone density values with the presence of Concentrated growth factors (Group 2) from baseline to first, third and sixth months are found to be 2.6, 5.7 & 5.7 respectively indicates a marked increase in density values around the implants (Table 7 & 8). Intergroup comparison shows a significant difference between both the groups starting from as early as the 1st month (Table 8 & 9).

The present study is in accordance with the similar studies conducted by Renu Kundu et al., with Platelet rich plasma (PRP) on bone and implant stability revealed marked improvement in implant stability. But the distinction is that, with CGF, the level of enhancement acquired is phenomenon and starts at the early stages of bone healing and osseointegration. Also the bone density is enhanced

above the baseline level, which could mean that bone mineralization is also enhanced by CGF. A more focussed study on that subject may shine light in this area.

CONCLUSION

The results of this study indicates that CGF is significantly better in improving bone density around the implants when comparing with non-CGF groups. Although, CGF showed improvement in bone mineralization, there is not much differences in crestal bone level changes on mesial and distal sides of the implants between two groups.

Though, the present study was done with a six month follow-up and the osseous regeneration was only measured indirectly over computer aided software (Digora), CGF did attribute to be a much simpler and a better platelet concentrate, in promoting osseous regeneration by increasing the density of bone around the implant from baseline to a much higher level. This attribute could be used in cases where bone mineralization is compromised. But the exact action of CGF on bone mineralization needs to be studied further.

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IMPLANT CASE RECORD

DEPARTMENT OF PROSTHODONTICS AND CROWN & BRIDGE

ADHIPARASAKTHI DENTAL COLLEGE & HOSPITAL

MELMARUVATHUR – 603319.

Case record for implant patient

Name : Date :

Age : Reg no :

Sex :

Address :

Tel no :

Chief complaint

Dental records

Oral tissue examination

Lips :

Cheeks :

Tongue :

Floor of the mouth :

Palate :

Tonsillar area :

Any other :

Periodontal examination

Gingivitis	: Mild / moderate / severe
Calculus	:
Recession	:
Periodontal pocket	:
Attrition	:
Abrasion	:
Erosion	:
Mobility	:
Occlusion	: class I / class II / class III
Hypoplasia	:
Impaction	:
Non vital	:
Fracture	:
Abscess	:
Ulcer	:
Caries	:
Missing teeth	:
Supernumerary	:
Others	:

Medical / dental questionnaire

1. Do you have any systemic disease? Yes / no
2. Have you been hospitalized during the previous 2 years? Yes / no
3. Do you take any medications on a daily basis? Yes / no
4. Are you currently pregnant? Yes / no / NA
5. Do you have any of the following problems?

Heart disease	yes / no
Circulatory disease	yes / no
Diabetes	yes / no
Liver disease	yes / no
Blood disorder	yes / no
Rheumatism	yes / no
Allergies	yes / no
Kidney disorder	yes / no
Thyroid disease	yes / no
Seizure disorder	yes / no
Lung disorder	yes / no
Gastrointestinal disorder	yes / no
Nervous disorder	yes / no
AIDS / HIV	yes / no

6. Do you experience excessive bleeding or bruise easily? Yes / no

Investigation advised:

Diagnostic X-ray:

Diagnostic models:

Pre-surgical treatment plan advised:

Pre-surgical treatment plan done:

Bone mapping / radiographic method:

Determination of length:

Determination of width:

Determination of bone density:

Implant

No of implants :

Length of the implant :

Width of the implant :

Provisional restoration

Temporary partial denture :

Resin bonded bridge :

Acrylic crown : Heat cure / cold cure

Any other :

Definitive prosthesis

Metal-ceramic crown :

All-ceramic crown :

Complete denture :

Any other :

Follow up and maintenance

At prosthesis delivery: Oral hygiene instruction yes / no

One month after prosthesis delivery

Review of home care techniques yes / no

Calculus removal and coronal polish yes / no

Three months later

Examination of tissues yes / no

Calculus removal and coronal polish yes / no

Establishment of a recall interval between 3 & 6 months

Complications

Surgical

Inferior alveolar nerve injury :

Lingual nerve injury :

Opening of nasal or maxillary sinuses :

Broken bur :

Oversized osteotomy :

Fetal air embolism :

Fractured mandible :

Hematoma :

Incision line opening :

Chronic pain :

Radiolucencies :

Infection :

Implant exposure :

Implant mobility :

Prosthodontic

Screw loosening and fracture :

Inaccurate abutment – framework interface :

Implant fractures :

Esthetic complication :

Framework fracture :

Pre operative

Intra operative

Implant placement

Provisional restoration

Post operative (Definitive prosthesis)

PATIENT CONSENT FORM

Participants name:

Address:

Title of the study:

"Randomized controlled study on effect of concentrated growth factors on crestal bone levels and peri -implant bone density in dental implants"

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at anytime, without giving any reason, without the normal medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the above study.

Signature of the participant: ---------- Date: ----------

பங்கேற்பாளரின் ஒப்புதல் படிவம்

பங்கேற்பாளரின் பெயர் :

முகவரி:

ஆய்வின் தலைப்பு :

"செறிந்த வளர்ச்சி காரணியின் விளைவாக பல் உள்வைப்பு முறையில் எலும்பு வரம்பு அளவின் தன்மையிலும், எலும்பின் அடர்த்தியிலும் ஏற்படும் தாக்கம் பற்றிய தற்செயலான கட்டுப்பாட்டு ஆராய்வு"

எனக்கு மேற்கண்ட ஆய்வைப் பற்றிய விவரங்களை எழுத்து மூலமாகவும் ,வாய்மொழியாகவும் விவரித்து கூறினார்கள். அதன்மூலம் நான் மேற்கண்ட ஆய்வை பற்றிய முழுமையான விவரங்களை (தகவல்களை) அறிந்துகொண்டேன். மேற்கண்ட ஆய்விற்கு என்னுடைய சிகிச்சை சம்பந்தமான தகவல்களை உபயோகித்துக் கொள்ள எனக்கு எந்த விதமான தடையும் இல்லை என்பதை தெரிவித்துக் கொள்கிறேன் .

இந்த ஆய்வில் பங்கேற்பதற்கு என்னுடைய முழுமையான சம்மதத்தை தெரிவித்துக் கொள்வதுடன் மட்டுமல்லாமல் இந்த ஆய்விலிருந்து எப்போது வேண்டுமானாலும் விலகிக்கொள்ள எனக்கு சுதந்திரம் உண்டு என்பதையும் அறிந்து கொண்டேன் .

பங்கேற்பாளரின் கையொப்பம்

INSTITUTIONAL ETHICS COMMITTEE AND REVIEW BOARD

ADHIPARASAKTHI DENTAL COLLEGE AND HOSPITAL

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This ethical committee has undergone the research protocol submitted by **Dr.V.C.Karthik,** Post Graduate Student, Department of Prosthodontics and crown & bridge under the title **"Randomized Controlled Study On Effect Of Concentrated Growth Factors On Crestal Bone Levels And Peri-Implant Bone Density In Dental Implants"** Reference No: **2014-MD-BrI-Ven-02,** under the guidance of Prof. **Dr.N.Venkatesan MDS.,** for consideration of approval to proceed with the study.

This committee has discussed about the material being involved with the study, the qualification of the investigator, the present norms and recommendation from the Clinical Research scientific body and comes to a conclusion that this research protocol fulfils the specific requirements and the committee authorizes the proposal.

Date: **Member secretary**